

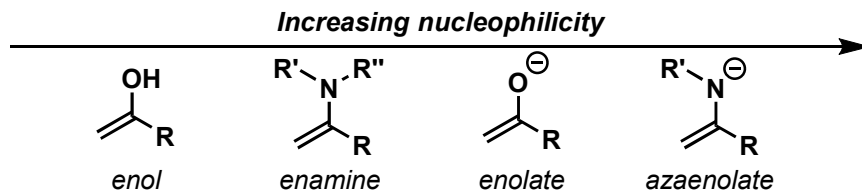
Chemistry 17: Section Handout 11

Topics: enol equivalents as nucleophiles, β -dicarbonyl compounds, decarboxylation, α -alkylation, aldol reaction/condensation, Mannich reaction, Claisen condensation, Michael addition

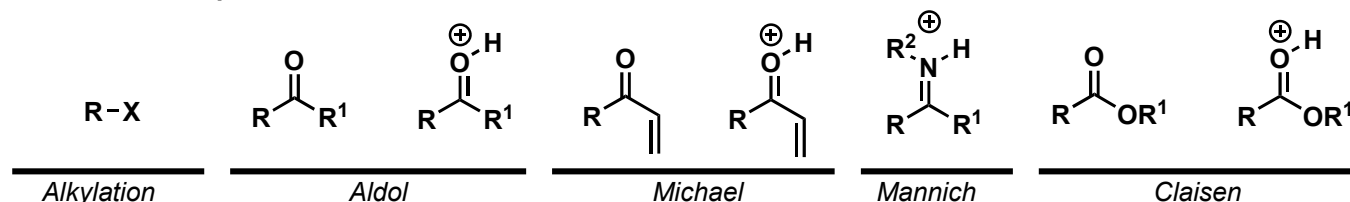
Key Concept Review

Reactivity of Enols and Enol Equivalents

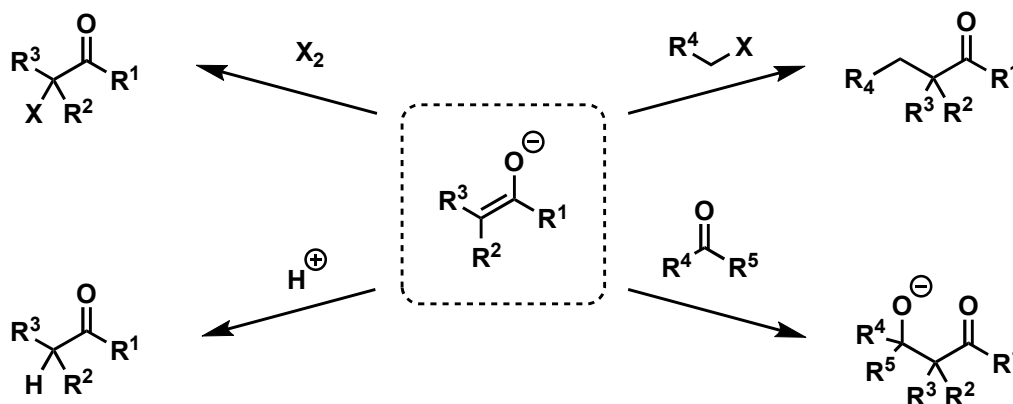
Enol equivalents: While the keto tautomer of carbonyl compounds is electrophilic, the enol tautomer is relatively nucleophilic. Enols themselves are weak nucleophiles, but related compounds display a range of nucleophile strengths (and open up the possibility for interesting reactivity).



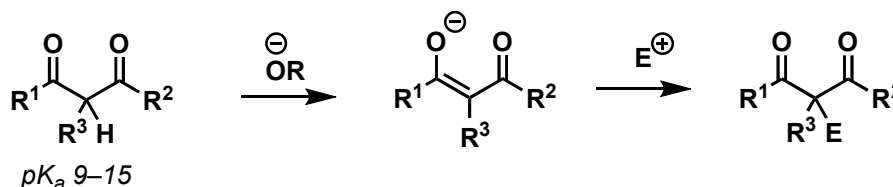
Potential electrophiles:



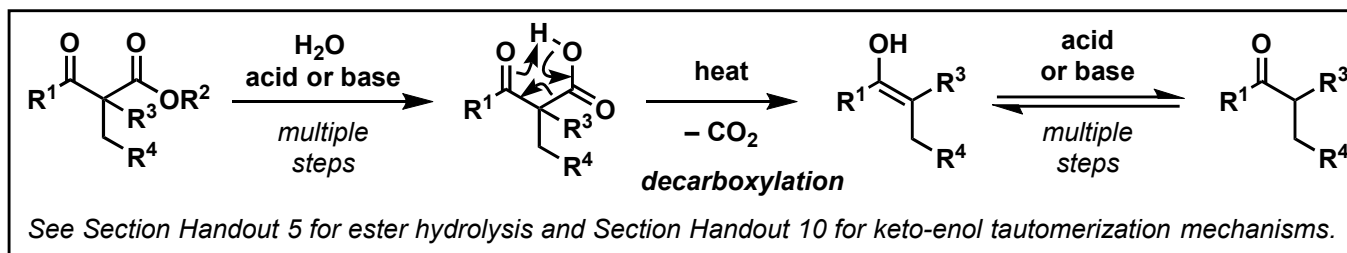
Reactivity of enolates: Enolates are among the most reactive and versatile enol equivalents. They can be made *in situ* with a weak base or pre-formed with a strong base like LDA (See Section Handout 10 for details), then used to attack a range of weak to moderate electrophiles.



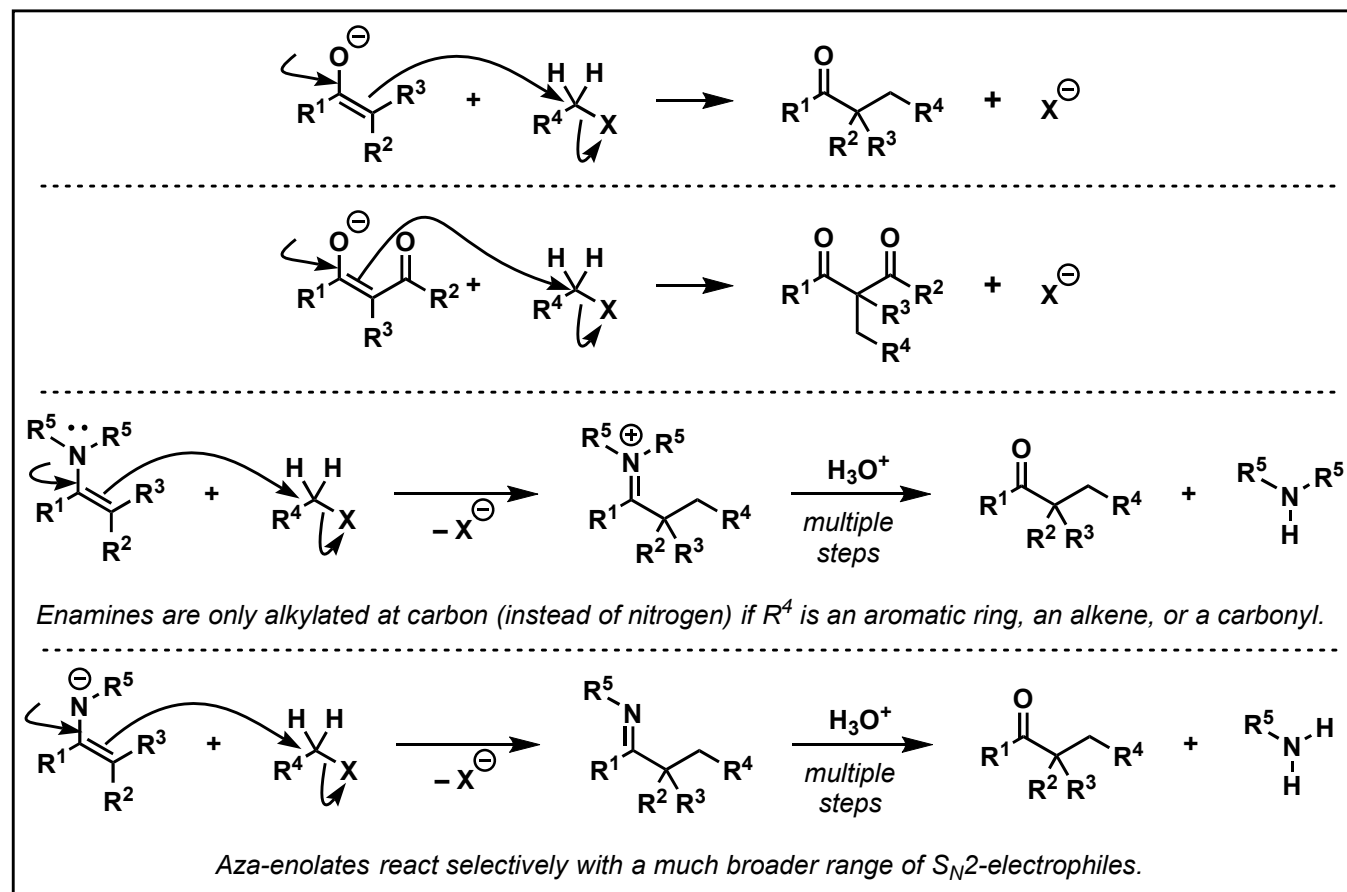
Reactivity of β -dicarbonyl compounds: Enolates of β -dicarbonyl compounds are far less basic than simple enolates, and "softer" due to charge delocalization. They react especially well with soft (S_N2 -type) electrophiles.



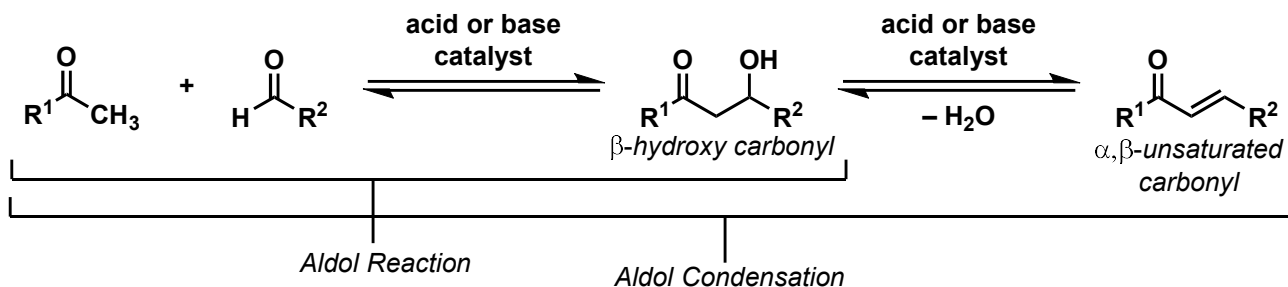
Often, reactions with β -ketoesters or β -diesters will be followed immediately by ester hydrolysis and decarboxylation to give the same product you would (hypothetically) get from reacting with a simple carbonyl. The decarboxylation is irreversible because CO_2 is a gas and leaves the reaction system.



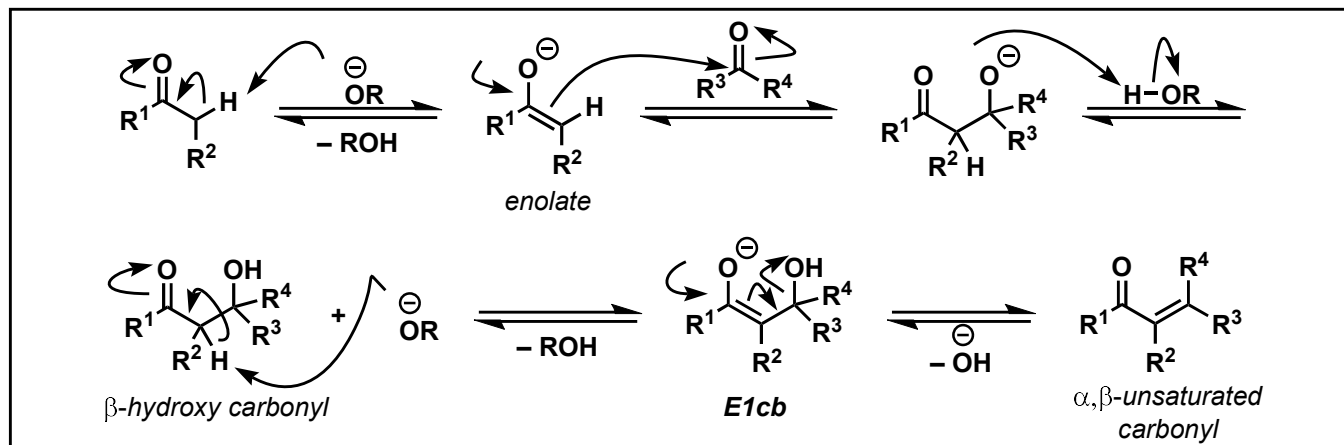
α-Alkylation Reaction: α-Alkylation involves the reaction of an enolate (especially enolates of β-dicarbonyl compounds), enamine, or aza-enolate with an sp³-carbon electrophile in an S_N2 reaction. These reactions produce carbonyl compounds that are branched at the α-position.



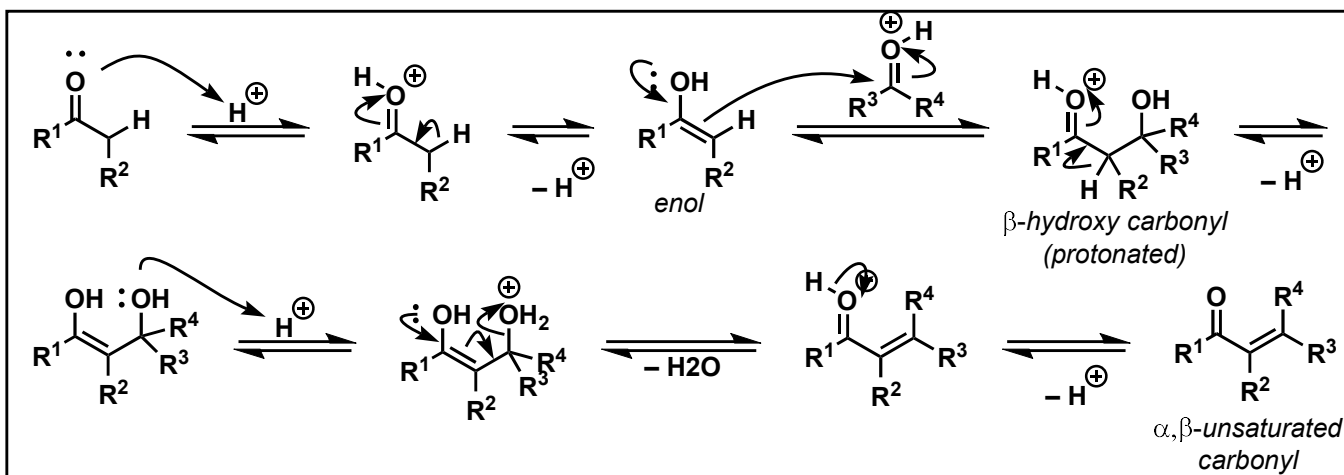
Aldol Reaction/Condensations: An aldol reaction is an acid- or base-catalyzed reaction involving the addition of an enol to an aldehyde or ketone to form a β-hydroxy carbonyl. An aldol condensation includes all the steps of an aldol reaction AND subsequent elimination of the β-hydroxy group to form an α,β-unsaturated carbonyl and water. While both the aldol reaction and aldol condensation are reversible, the equilibrium can be driven toward the condensation product by removing water. The reverse reaction is known as a “retro-aldol”.



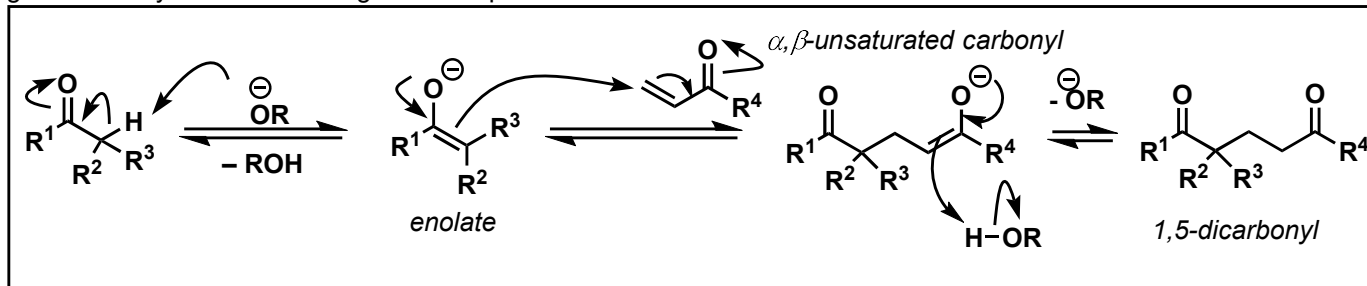
Base-catalyzed aldol condensation: A base catalyst can be used to form the enolate ion intermediate in small equilibrium concentrations *in situ*, or stoichiometric LDA can be used to pre-generate the enolate. The strongly nucleophilic enolate can then react with a weakly electrophilic ketone or aldehyde to form a β -hydroxy carbonyl. The reaction can stop there, or elimination from the β -hydroxy carbonyl can occur by an E1cb mechanism to form the α,β -unsaturated carbonyl.



Acid-catalyzed aldol condensation: An acid catalyst can be used to form the enol tautomer in small equilibrium concentrations *in situ*. The weakly nucleophilic enol can then react with strongly electrophilic protonated ketone or aldehyde to form a β -hydroxy carbonyl. The reaction generally continues, and elimination from the β -hydroxy carbonyl can occur by an E1cb-like mechanism to form the α,β -unsaturated carbonyl.

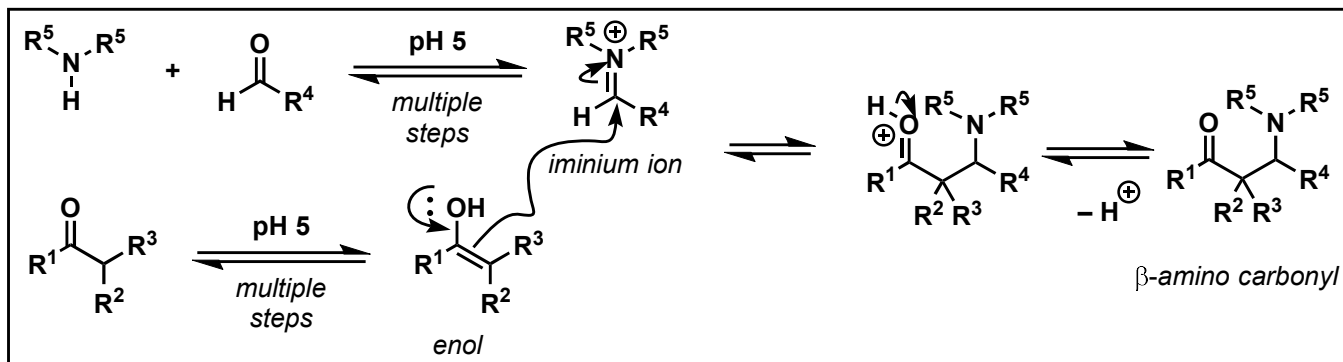


Michael Reaction: The Michael reaction differs from all the previous examples in that the electrophile is an α,β -unsaturated carbonyl compound (aldehydes, ketones, or esters are most common) and attack of the enolate nucleophile occurs at the β -carbon rather than at the carbonyl group, so-called “conjugate addition”. The regioselectivity is driven by orbital effects, i.e. the favorable soft-soft interaction between the enolate HOMO and the enone LUMO which has its largest coefficient on the β -carbon. The standard mechanism involves base catalysis: The enolate formed by conjugate addition to the α,β -unsaturated carbonyl is protonated to regenerate the carbonyl group. Dicarbonyl enolates or enamines can be used as the nucleophile. The Michael generates a 1,5-dicarbonyl compound, and is often carried out in a sequence where it is followed by an Aldol reaction to generate a cyclohexenone ring. This sequence is known as the Robinson annulation.

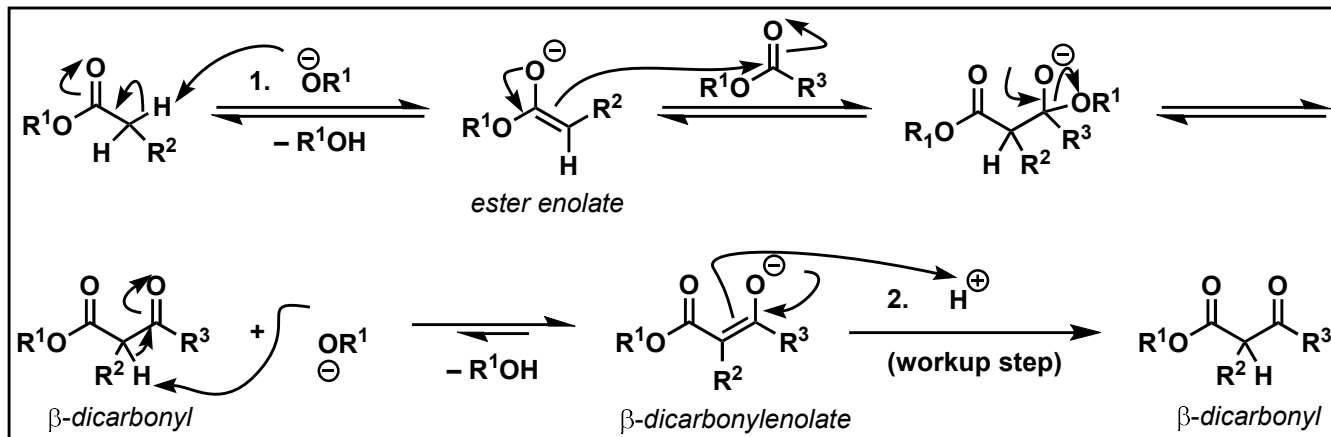


The Mannich and Claisen reactions will be covered in lectures 31 and 32 after section 11 but are included here as this is the last section handout. **All content before this point will be on Exam 3!**

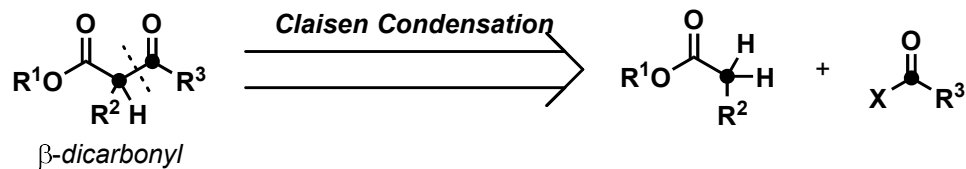
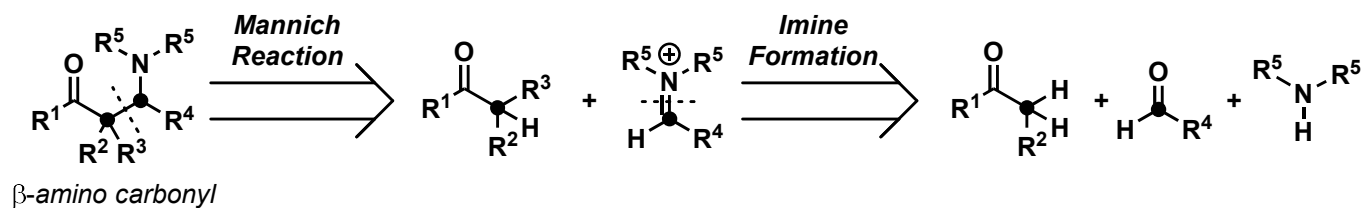
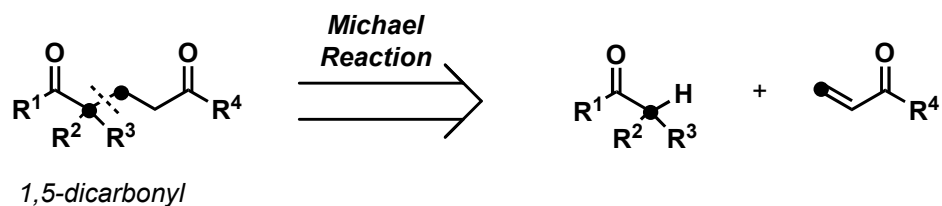
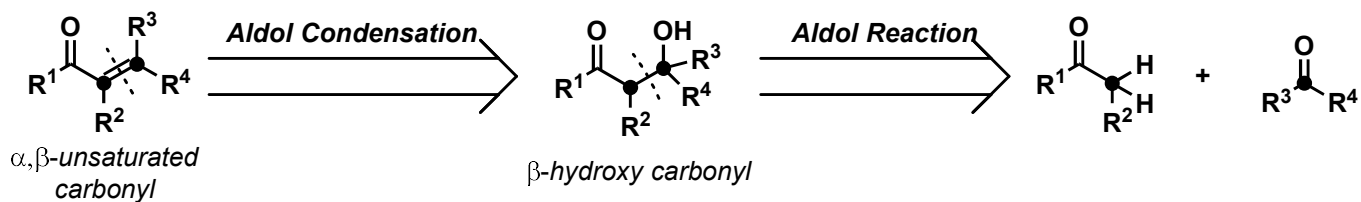
Mannich Reaction: The Mannich reaction is completely analogous to the acid-catalyzed aldol reaction, except the electrophile is an iminium ion instead of a protonated carbonyl. Often these iminium ions are generated *in situ* by combining an amine with a highly electrophilic carbonyl compound (to form the iminium ion) at pH 5 along with a second, less-electrophilic carbonyl compound (to form the enol nucleophile). The products of the Mannich reaction are β -amino carbonyls.



Claisen Condensation: Claisen condensations are analogous to the base-catalyzed aldol reaction, except the electrophile is a carboxylic acid derivative (usually an ester) instead of an aldehyde or ketone. As such, an acyl-transfer (addition-elimination) reaction occurs to form a β -dicarbonyl product. While the Claisen condensation is reversible, the equilibrium is driven toward the condensation product under basic reaction conditions due to irreversible deprotonation of the acidic α -position of the β -dicarbonyl product. As such, a stoichiometric amount of base must be used in the first step, and an acidic workup (occurring in a separate step after the Claisen condensation is over) is necessary to isolate the neutral β -dicarbonyl product.

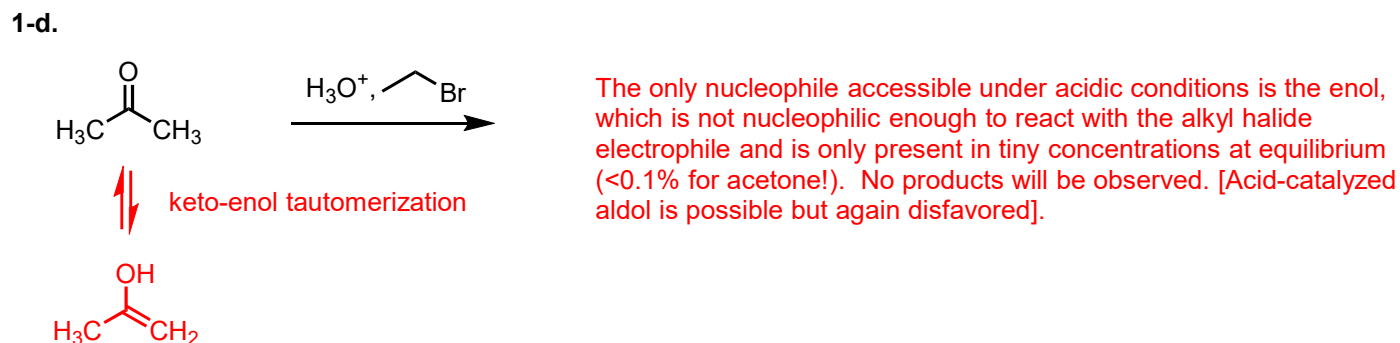
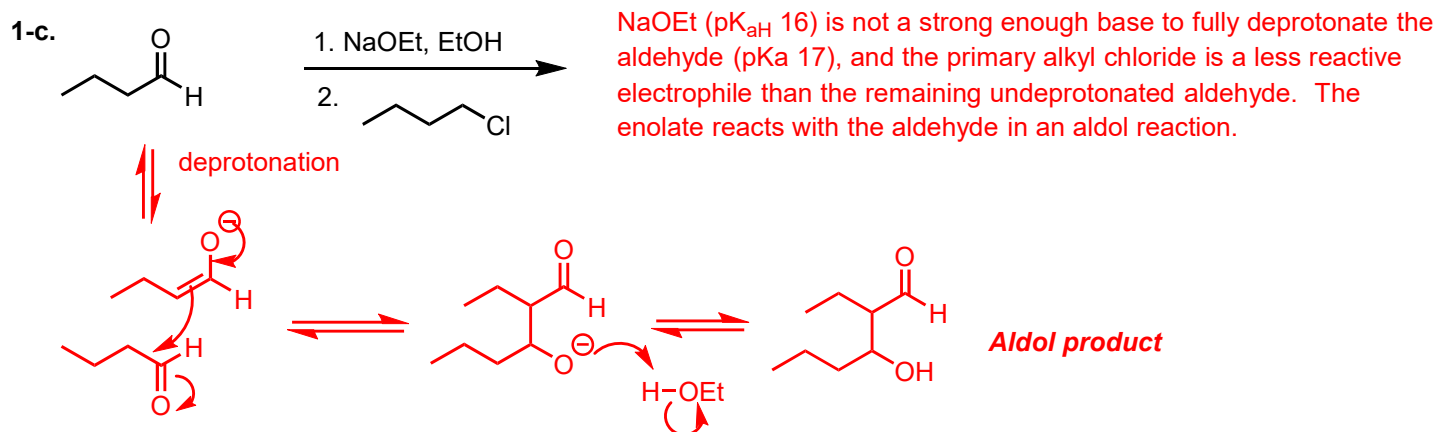
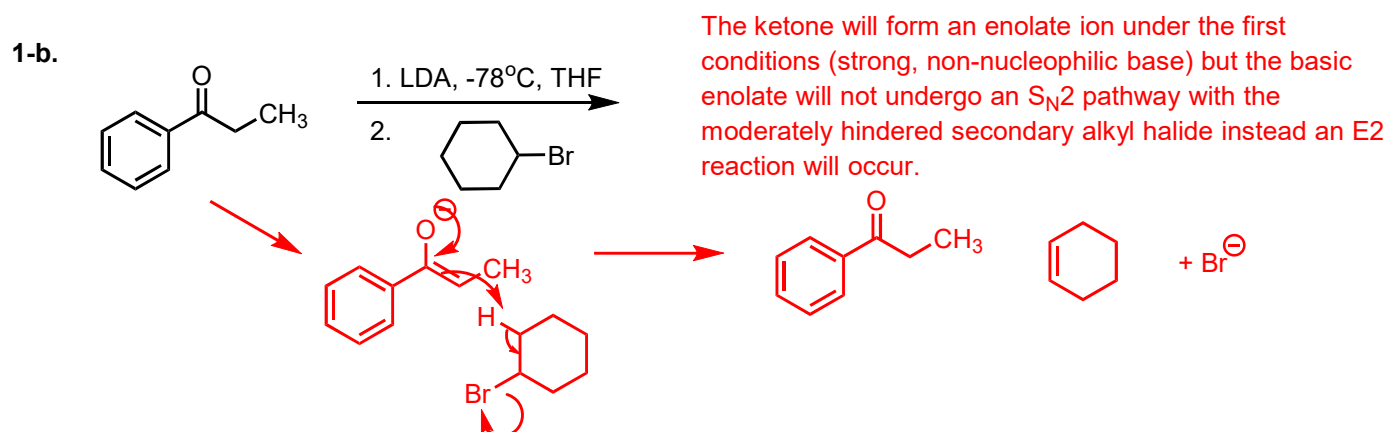
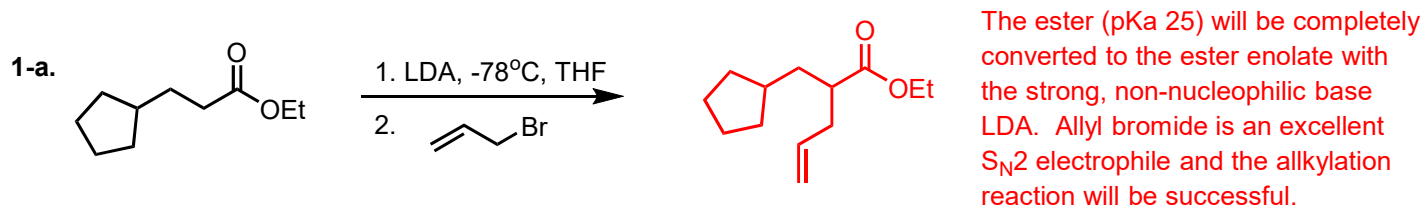


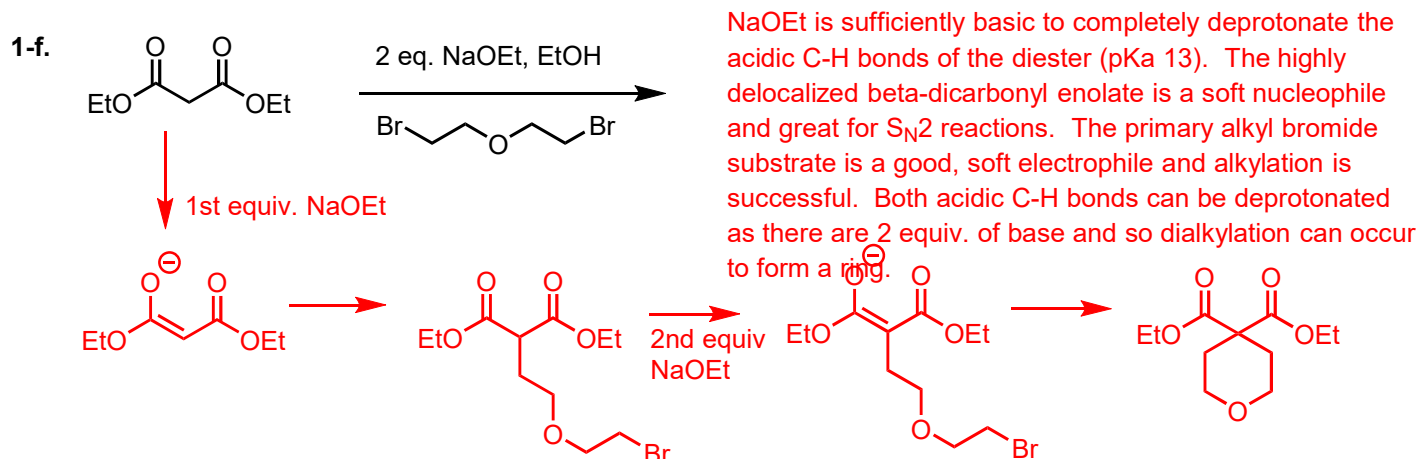
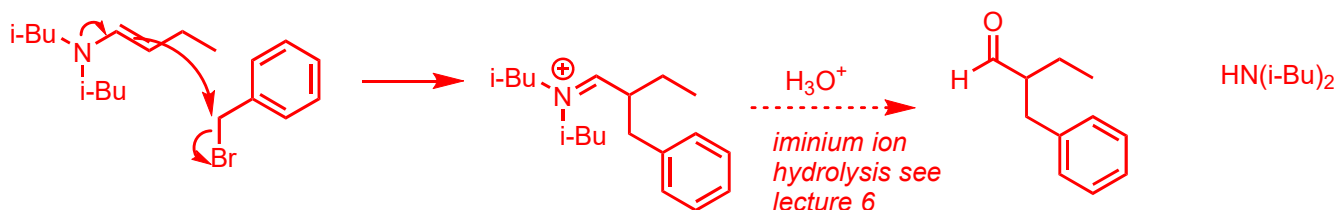
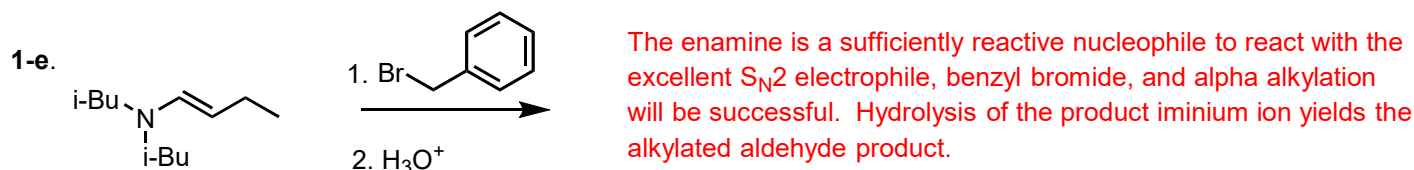
Summary of Retrosynthetic Disconnections in Complex Carbonyl Mechanism Problems:



Workshop Problems

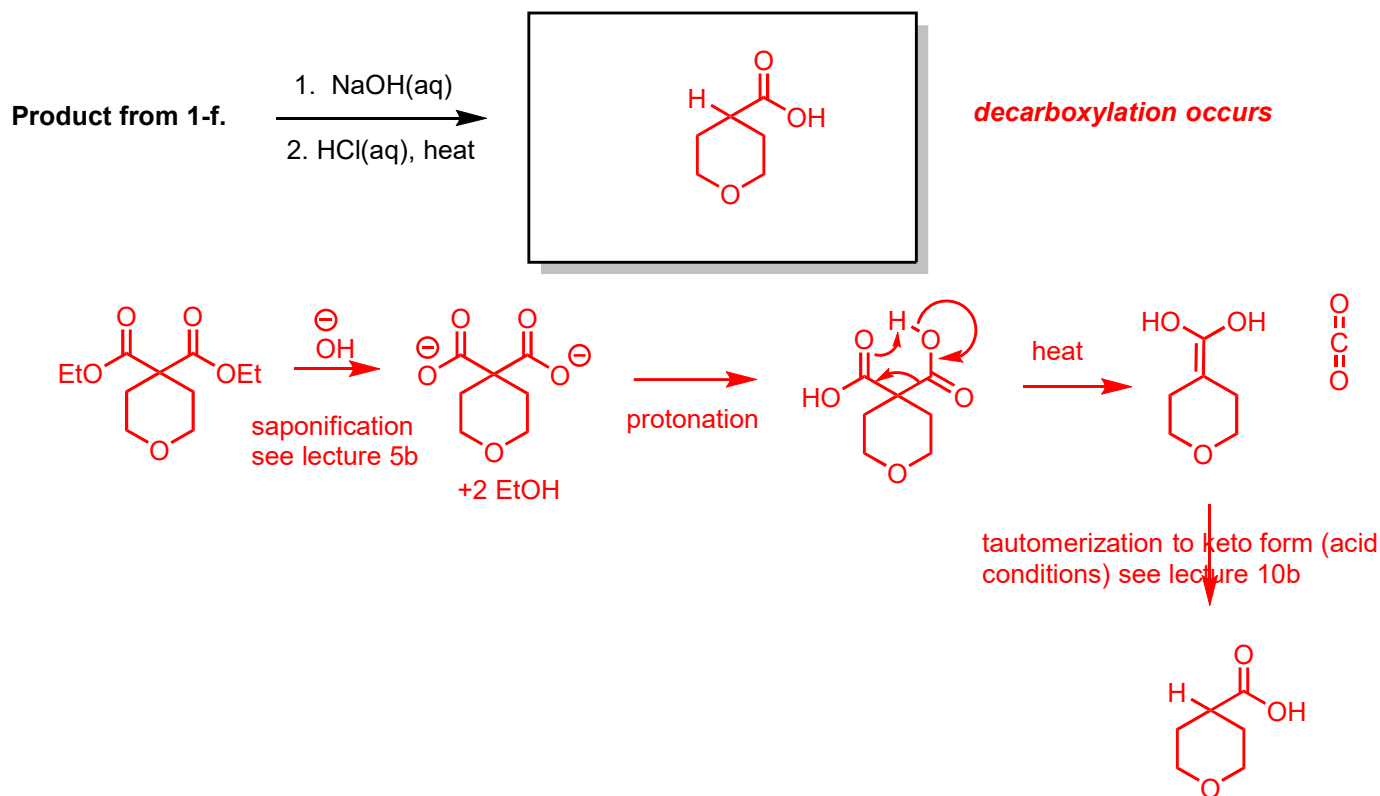
Workshop Problem 1: Proper choice of reaction conditions is critical for the success of alpha-alkylation reactions of carbonyl compounds. For each of the reactions, decide whether the alpha-alkylation reaction will be successful and explain why or why not in each case. Draw the product that would form, either the alpha-alkylation product or another product if a different reaction occurs.



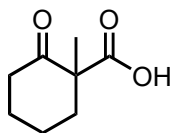


Workshop Problem 2: Decarboxylation

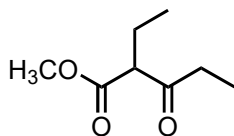
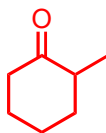
2-a. Predict the product and draw the mechanism for the reaction when the product from 1-f. is subjected to the reaction conditions listed.



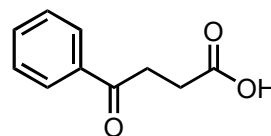
2-b. Decarboxylation reactions have certain structural requirements. Predict whether the compounds shown below will undergo decarboxylation upon heating in neutral solution and explain why or why not.



Yes. Compound is a carboxylic acid with a carbonyl group beta. Product will be:



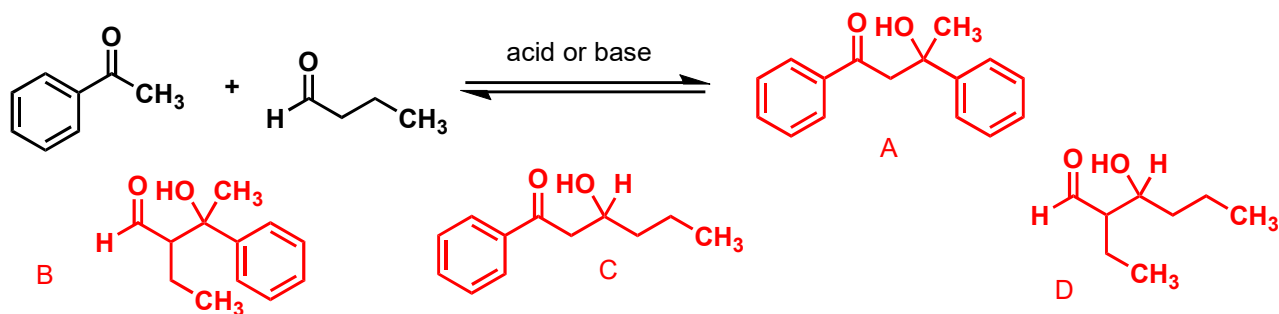
No. Compound needs to be a carboxylic acid. Saponification of the ester followed by protonation is required before decarboxylation can occur



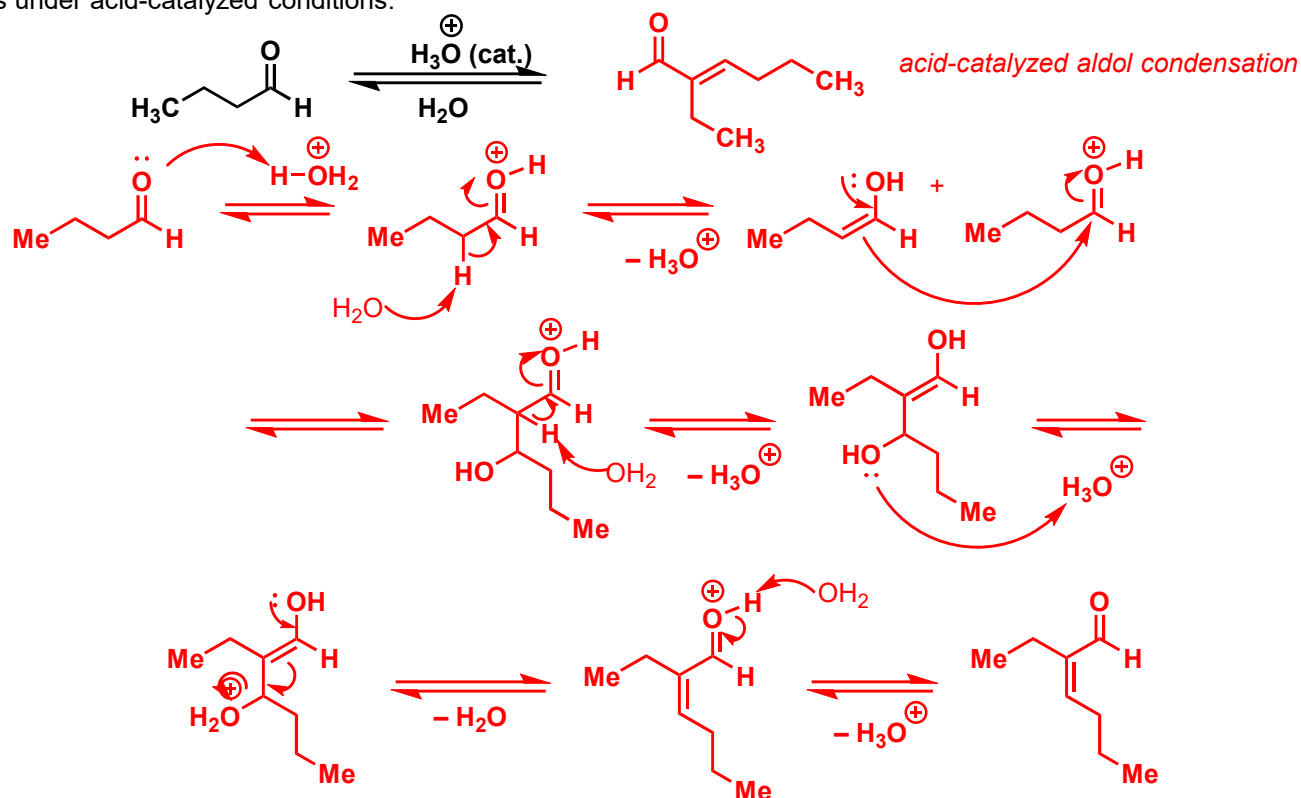
No. The second carbonyl group needs to be beta (or 1,3) to the carboxylic acid group to allow for the 6-ring Transition state necessary for decarboxylation. This is a 1,4 dicarbonyl compound.

Workshop Problem 3: The Aldol reaction and condensation

3-a. Draw all possible single aldol addition reaction products resulting from the combination of the reagents below. You do not need to show the condensation products or represent stereochemistry.

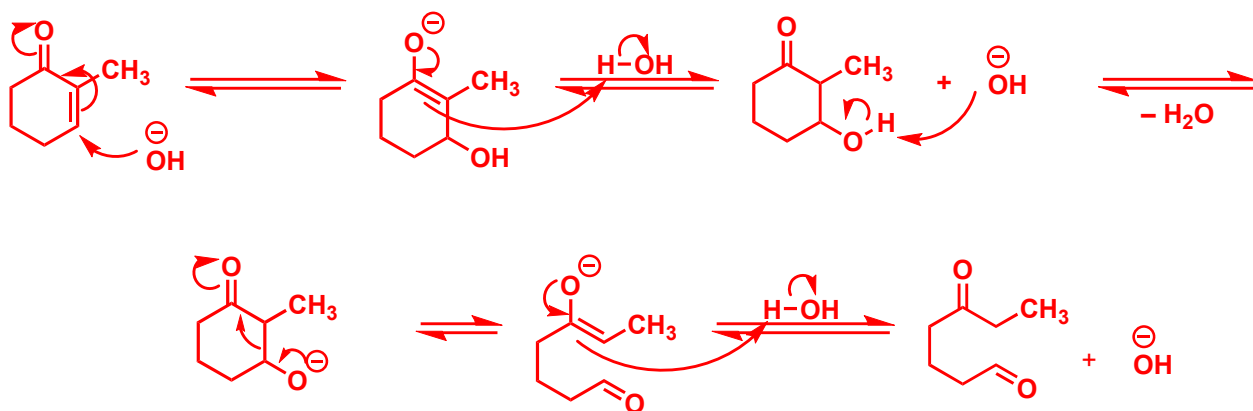
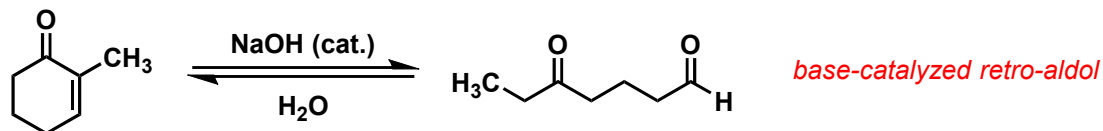


3-b. Predict the product and draw the mechanism for the aldol condensation product if just the aldehyde from 2-a reacts under acid-catalyzed conditions.

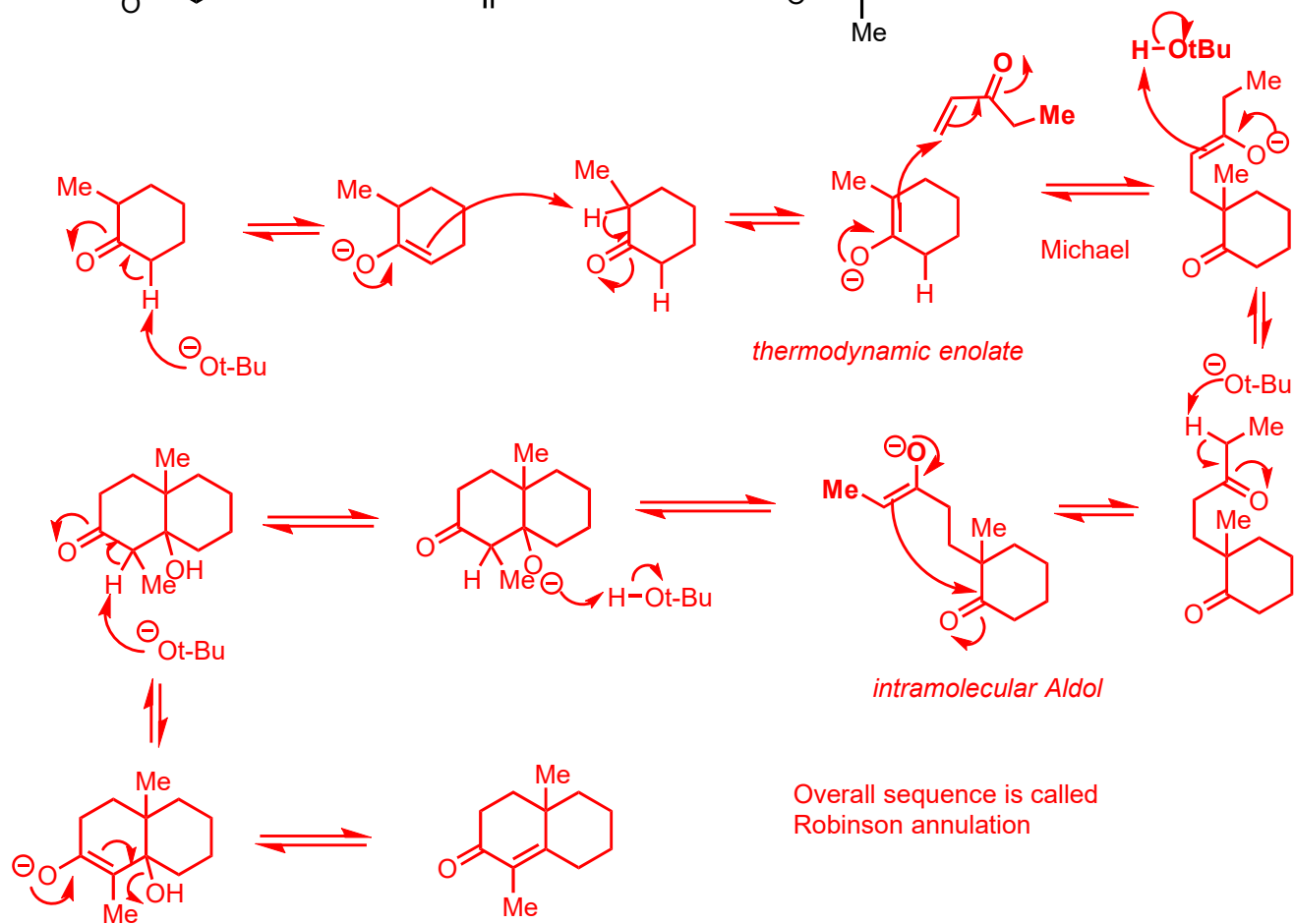
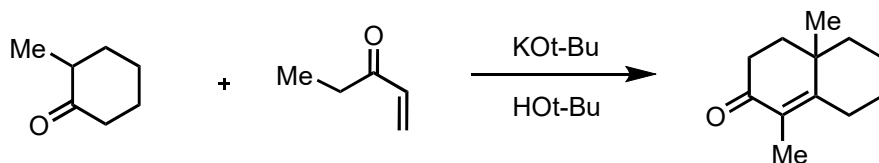


Workshop Problem 4: Aldol, Retro-Aldol and Michael Reactions
 Draw the mechanisms of the reactions below to give the products shown.

4-a.



4-b.

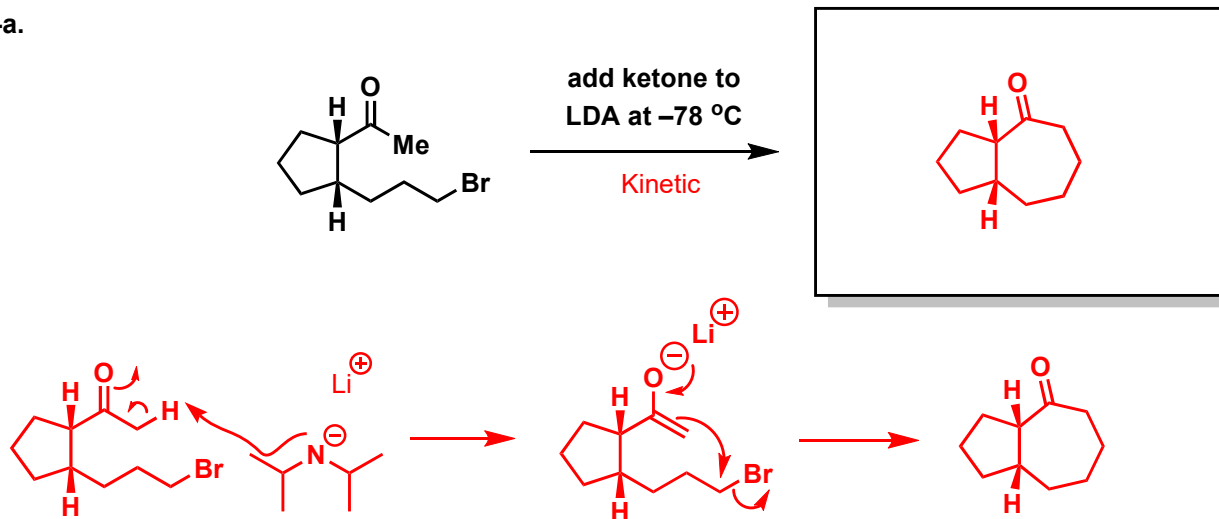


Practice Problems

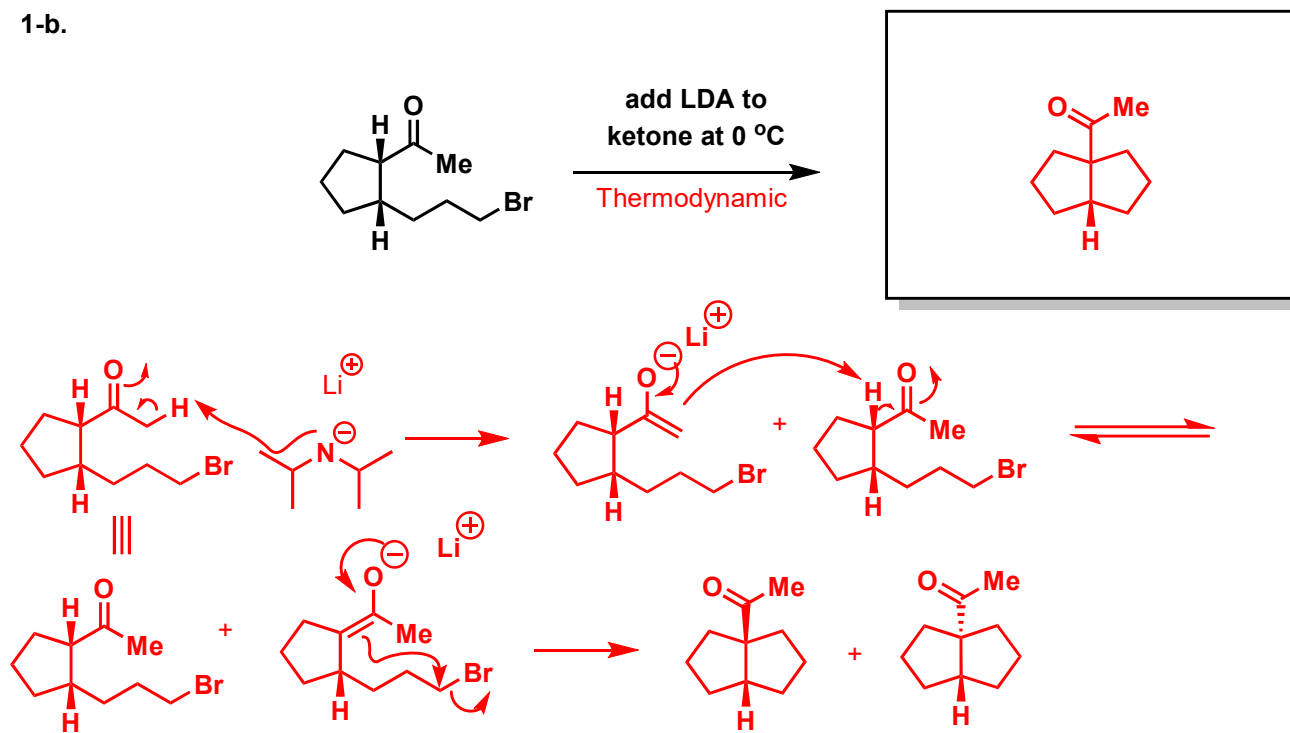
Skillbuilder Problem 1: Reactivity and Regioselectivity of Pre-Formed Enolates

Under controlled reaction conditions, kinetic or thermodynamic enolates may be formed and alkylated selectively. For each set of conditions below, indicate whether the kinetic or thermodynamic enolate is formed. Propose a mechanism for enolate formation and subsequent alkylation, and use your mechanism to predict the structure of the major alkylation product formed in each case.

1-a.

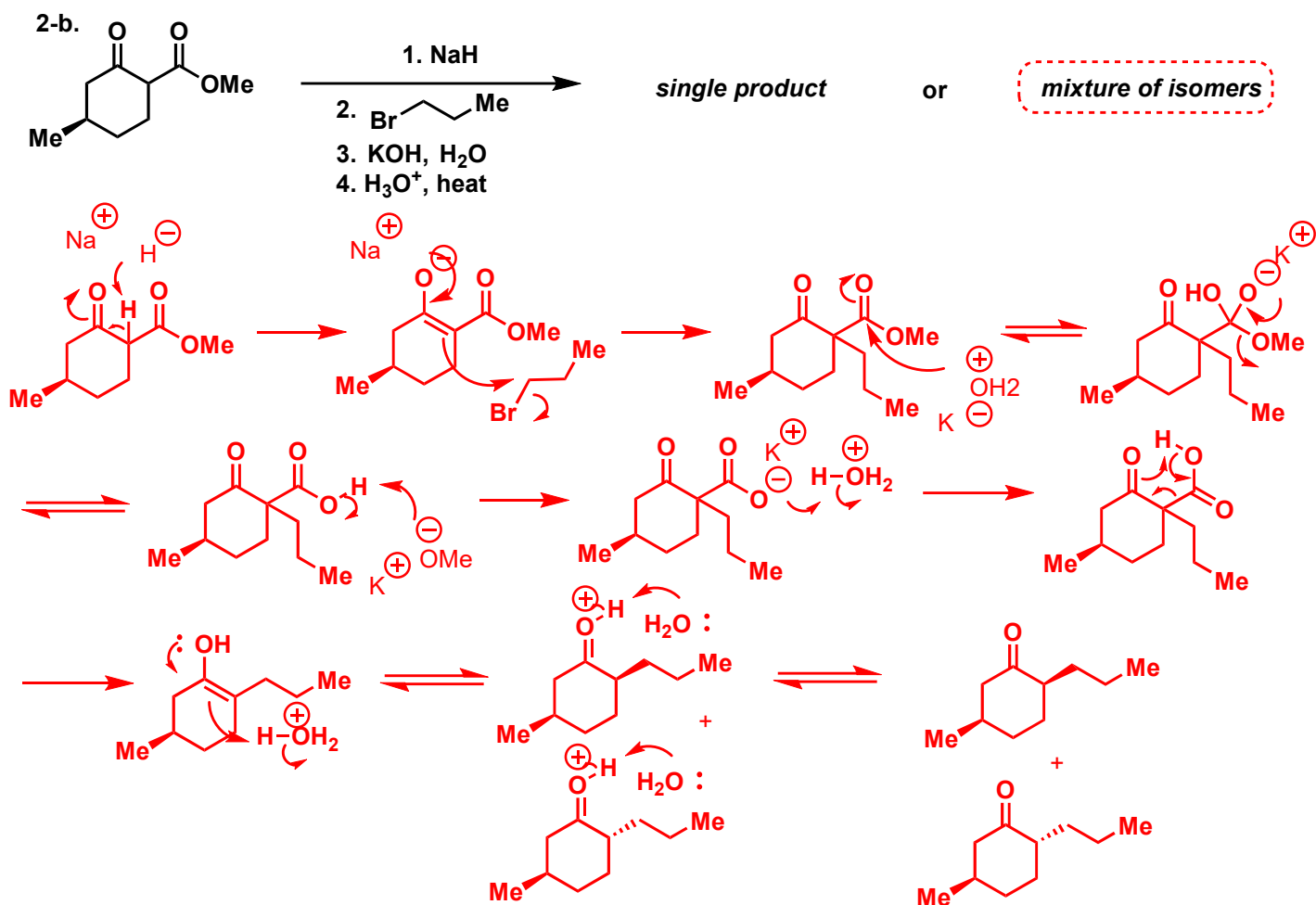
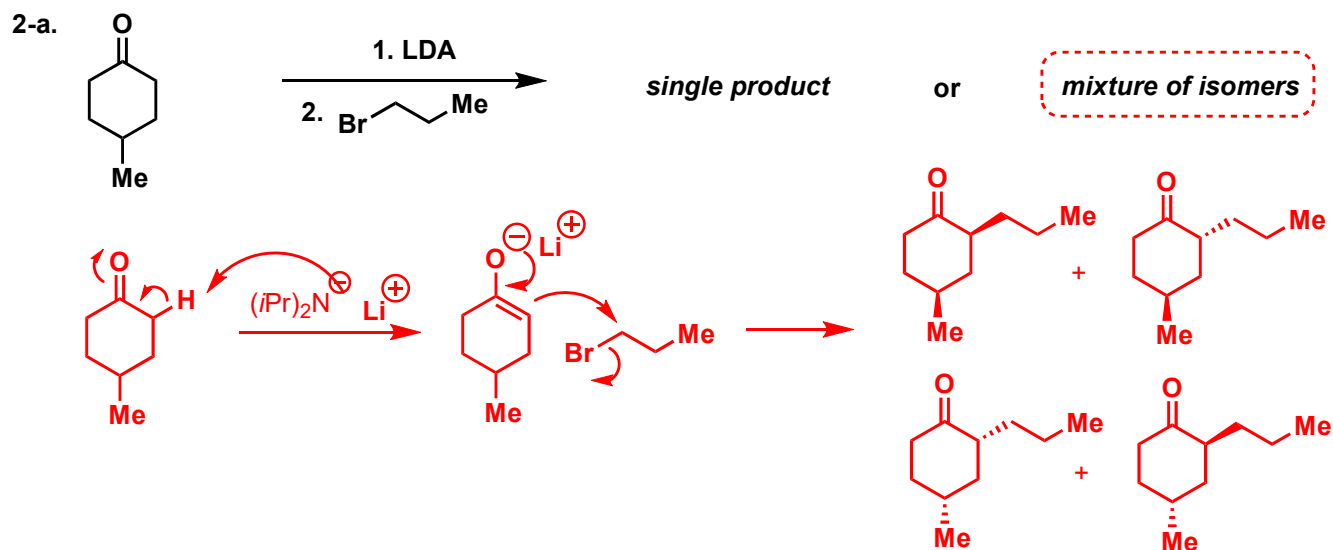


1-b.



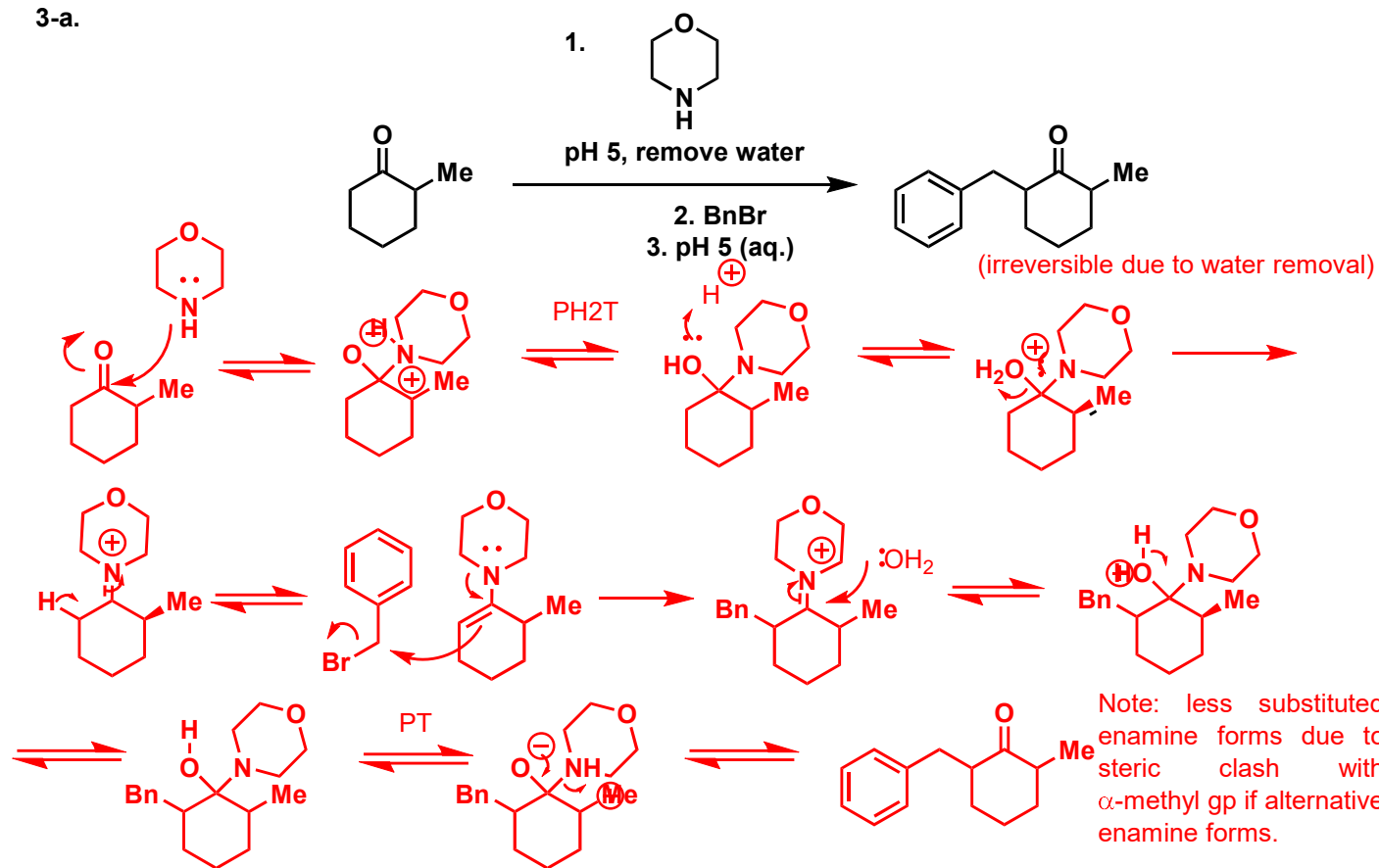
Skillbuilder Problem 2: Reactivity and Regioselectivity of Pre-Formed Enolates

The enolates derived from two related ketones both readily undergo alkylation under the conditions shown below to produce isomeric products. For each set of conditions, propose a mechanism for the entire reaction sequence, using curved arrows to represent the redistribution of electron density in each step.

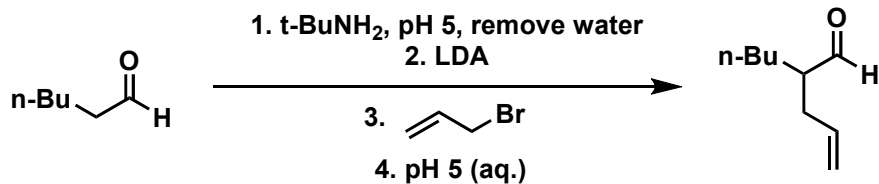


Skillbuilder Problem 3: Alkylation Reactions

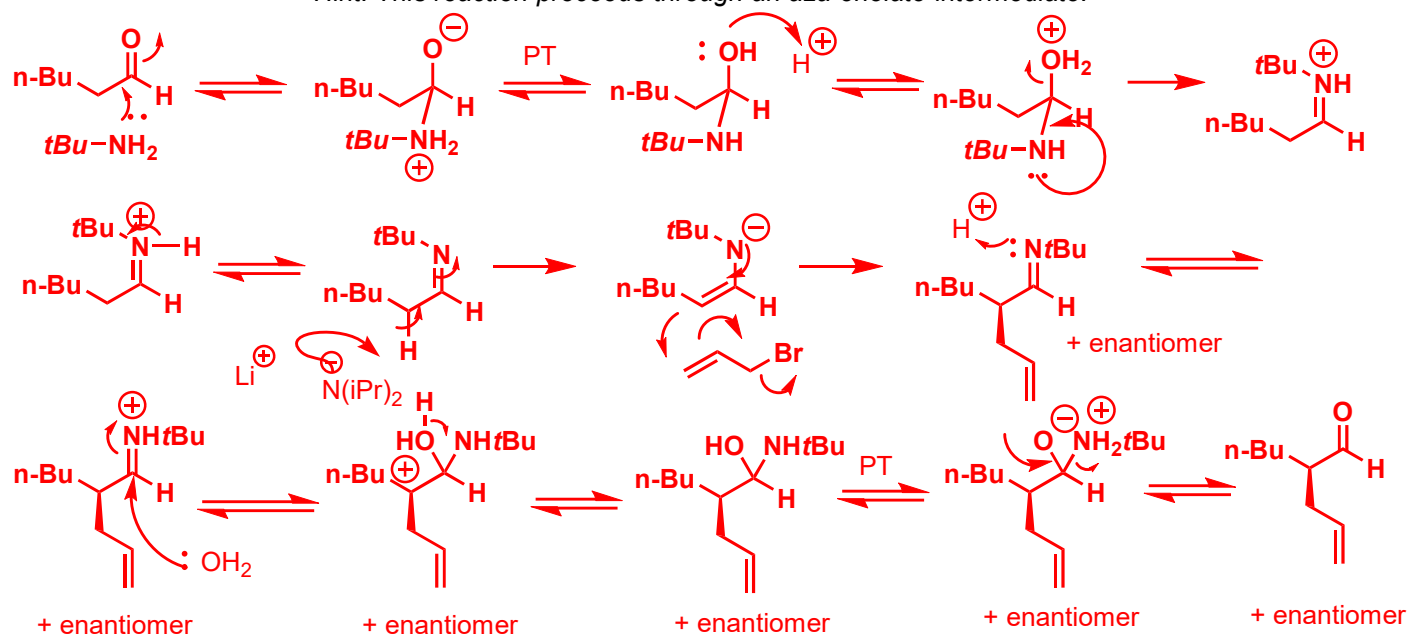
3-a.



3-b.



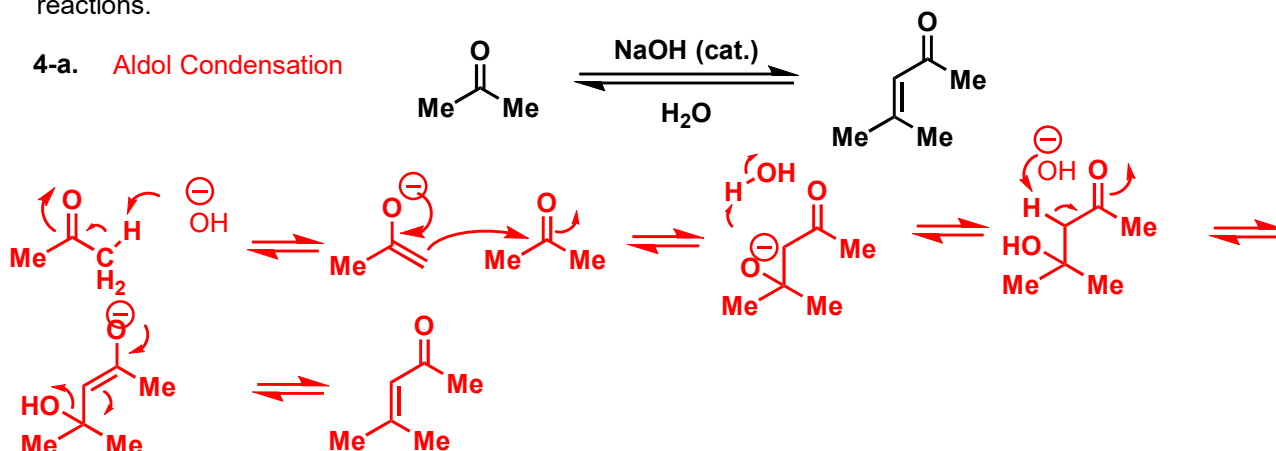
Hint: This reaction proceeds through an aza-enolate intermediate.



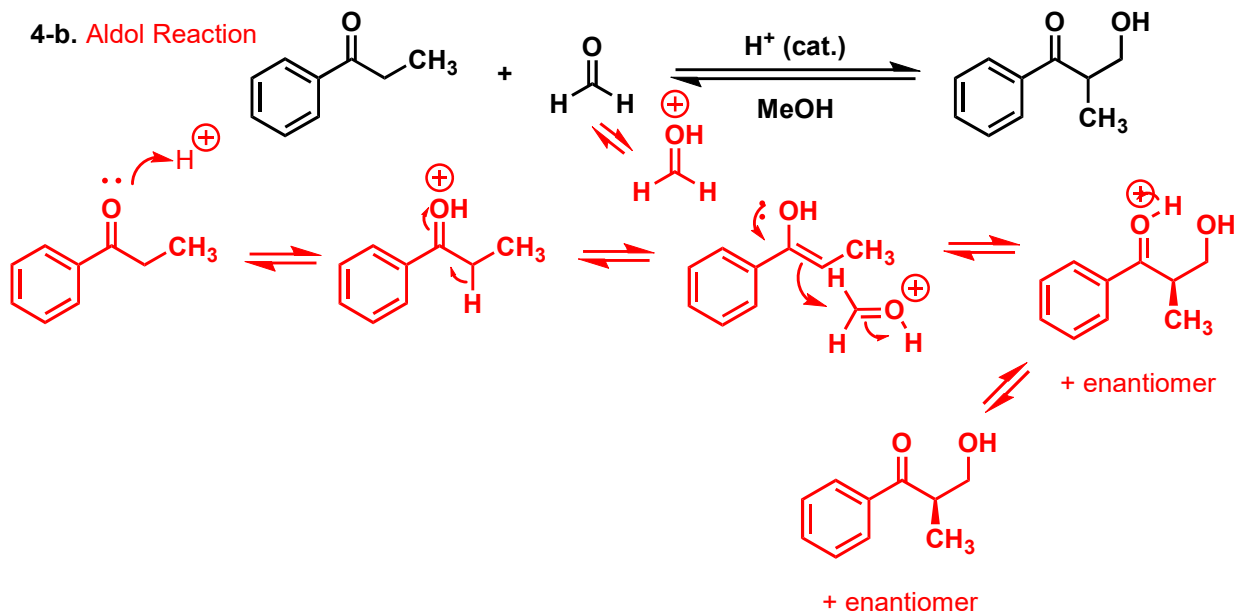
Skillbuilder Problem 4: Alkylation and Aldol Mechanisms

Inspect each of the transformations below and identify which type(s) of reaction(s) (alkylation, aldol reaction, aldol condensation, retro-aldol) is/are operative. Then propose a mechanism for each transformation, using curved arrows to represent the redistributions of electrons in each step. Consider the stereochemical outcomes of your reactions.

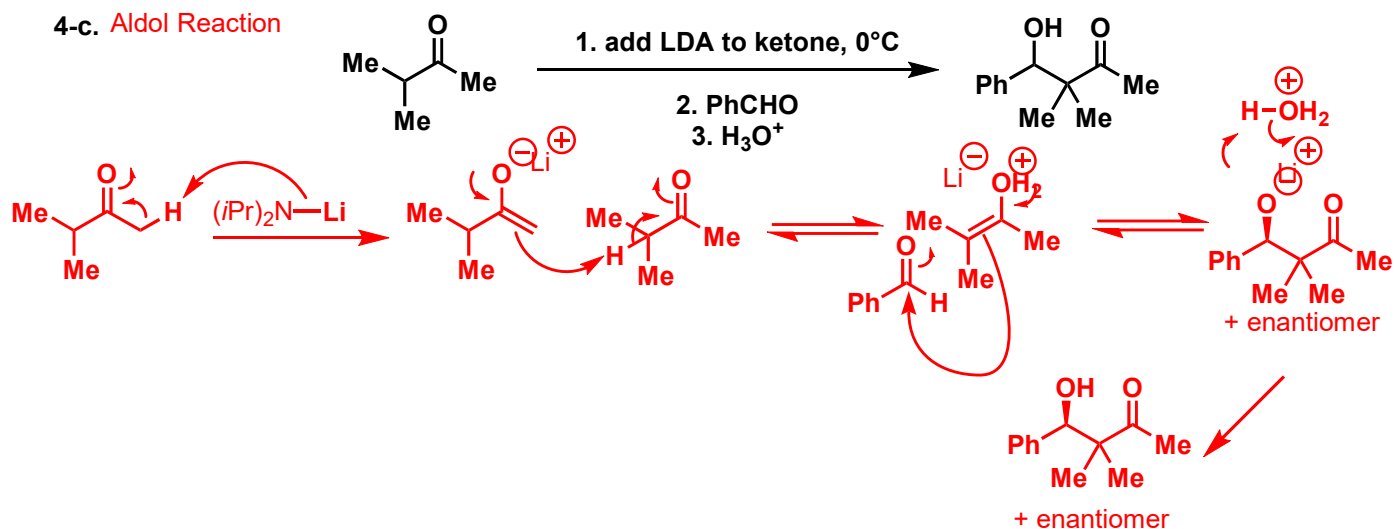
4-a. Aldol Condensation



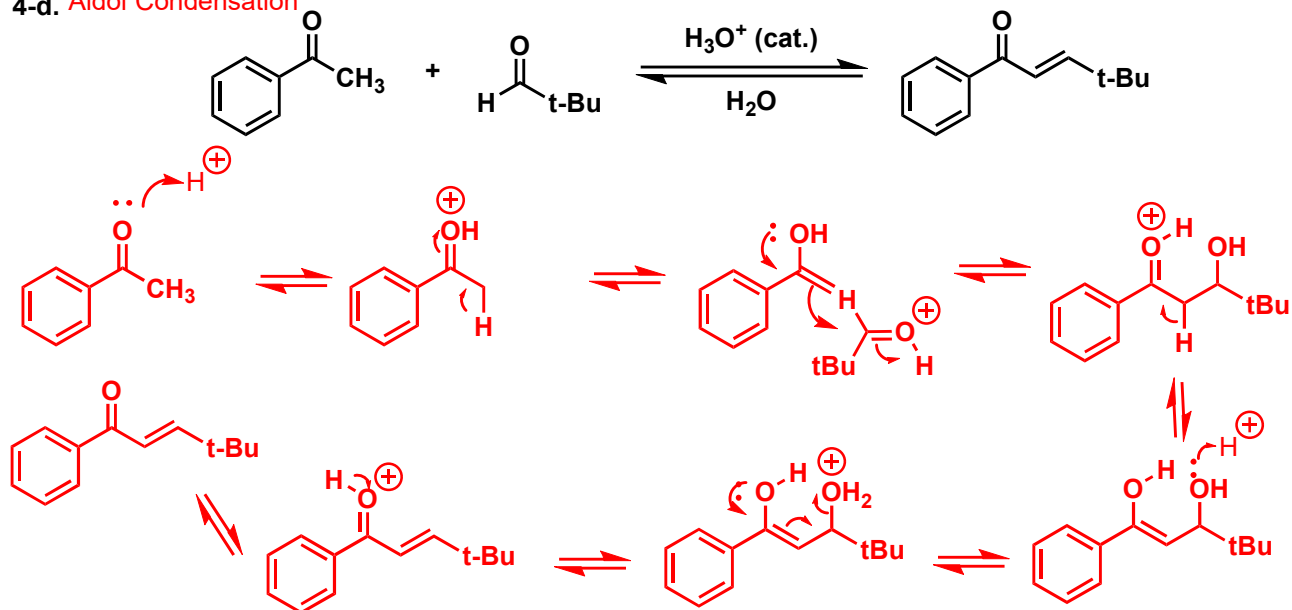
4-b. Aldol Reaction



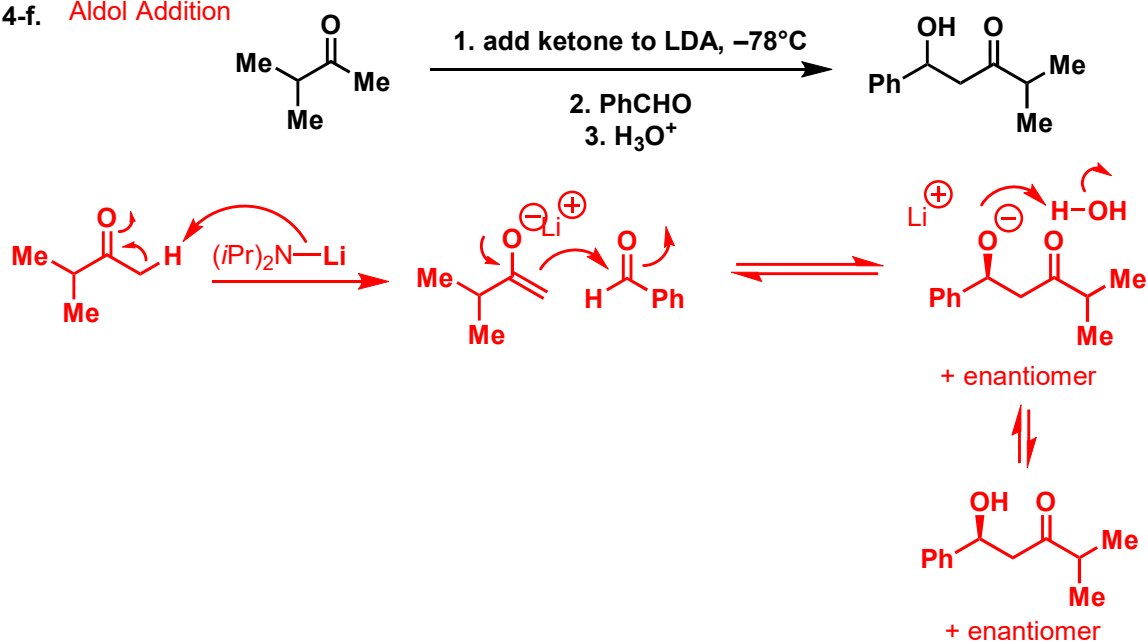
4-c. Aldol Reaction



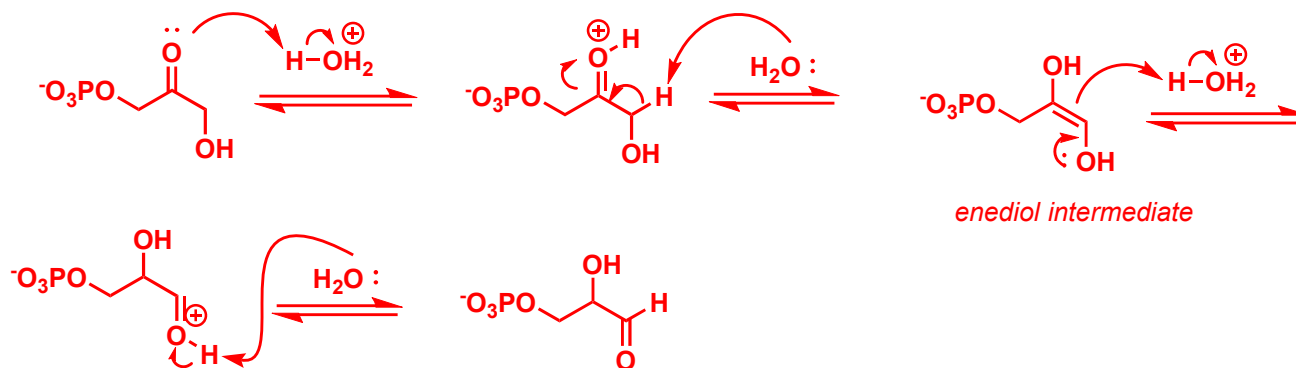
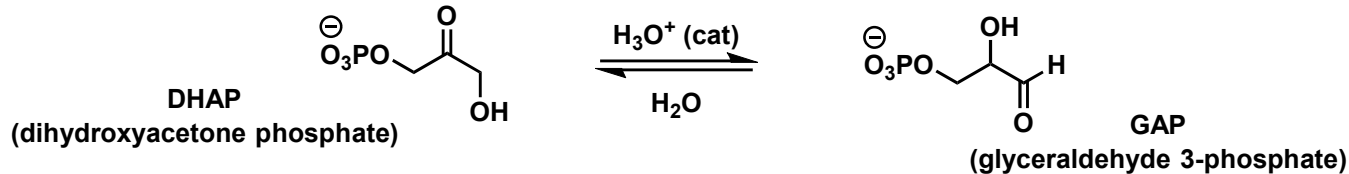
4-d. Aldol Condensation

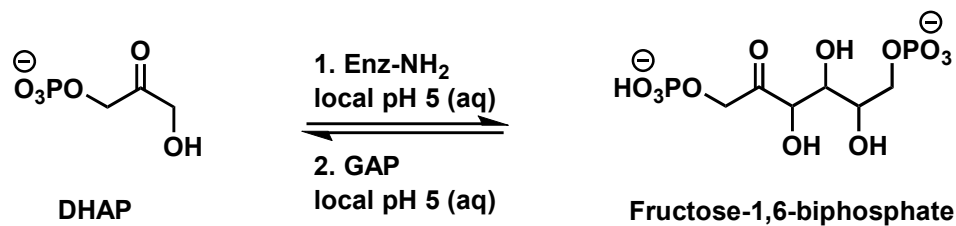


4-f. Aldol Addition

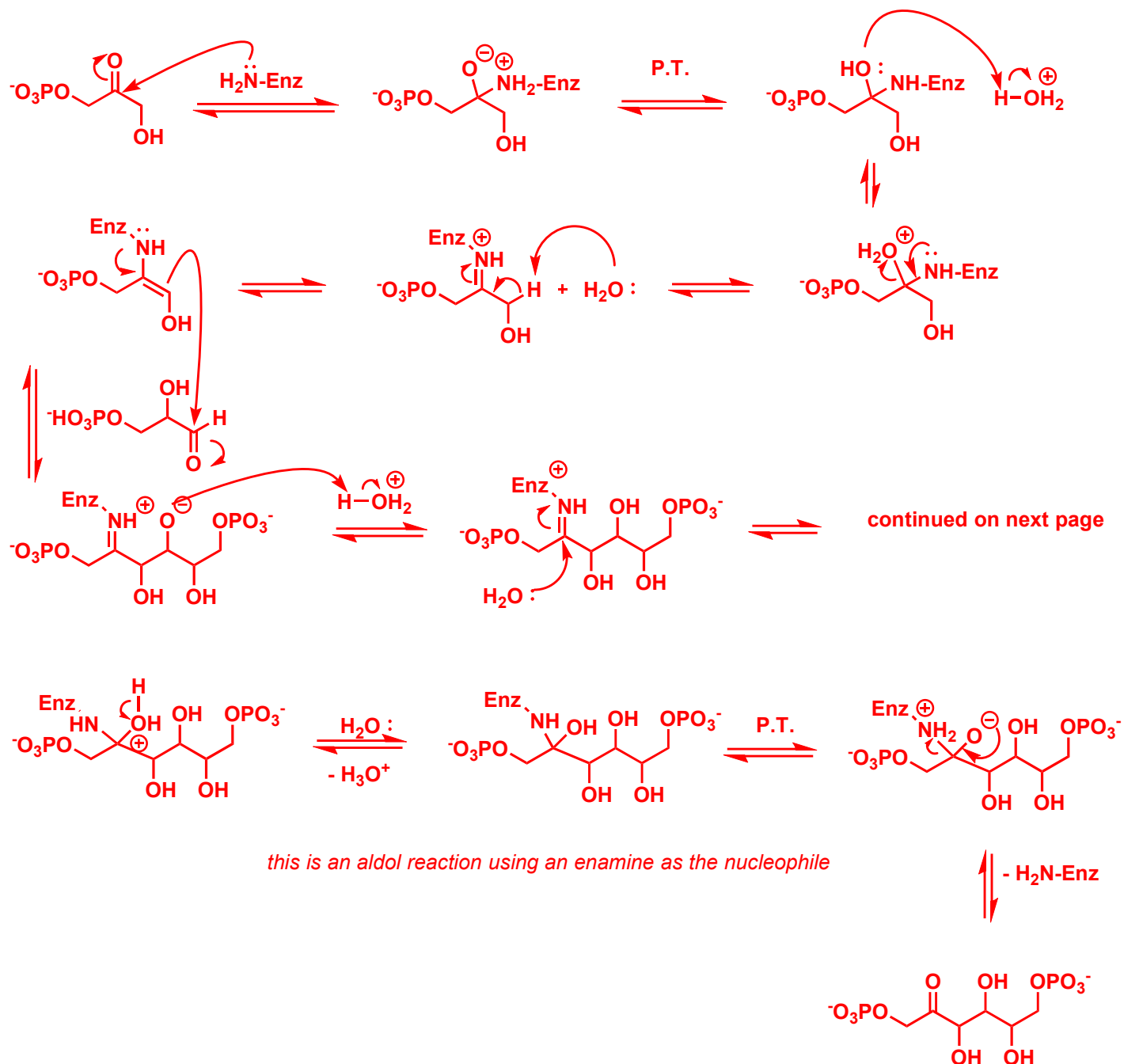


Challenge Problem 1: The chemistry in the reactions below is central to the biosynthesis of sugars. Propose a mechanism for each step of the transformation (3 total steps) shown below using the curved arrow formalism. You do not have to account for stereochemistry. [Note the phosphate groups play no direct role in the mechanisms but are present in the biological substrate.]





Note: Enz-NH₂ represents the amine side chain on an enzyme responsible for catalyzing this transformation.



Retro-Aldol/ Aldol Condensation

The diagram illustrates the mechanism of the retro-aldol/aldol condensation reaction. The reaction is shown at the top: bicyclo[6.1.0]non-2-en-9-one reacts with NaOH (cat.) in H₂O to form bicyclo[6.1.0]non-2-one. The mechanism proceeds through several steps, shown in red:

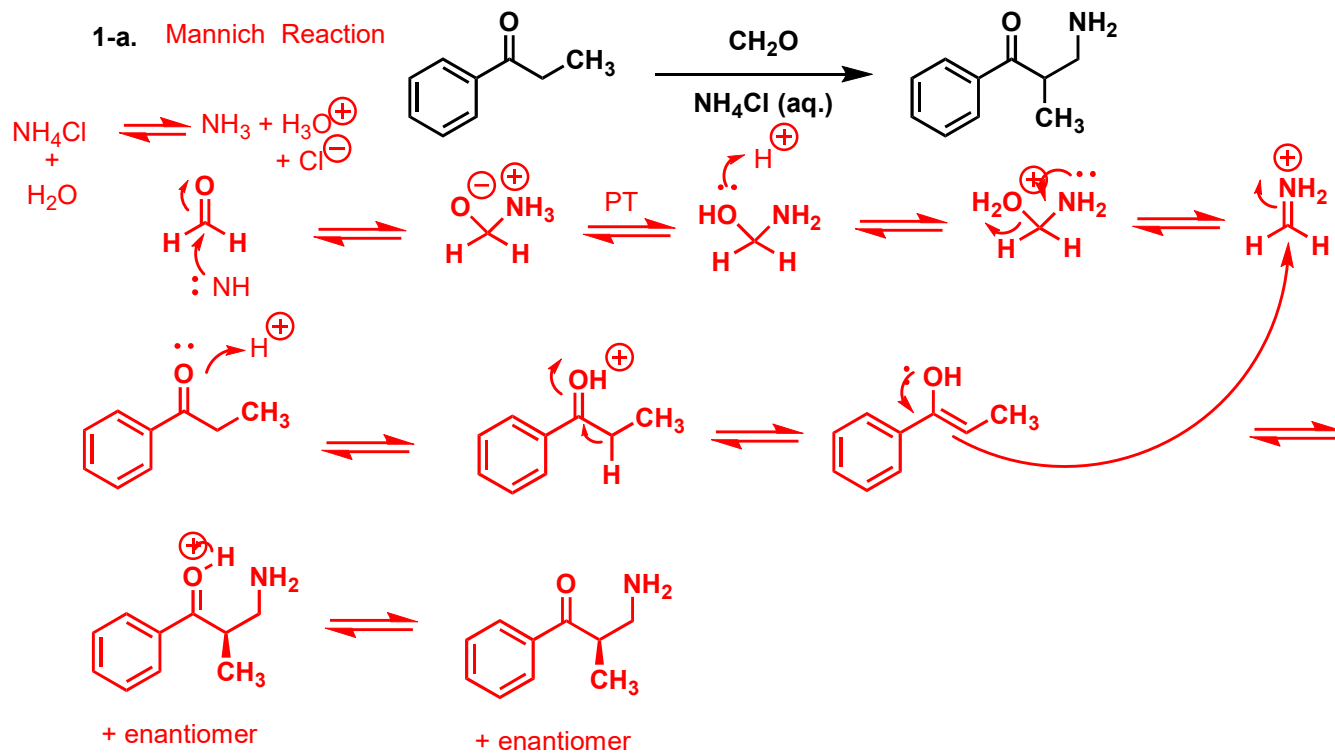
- Deprotonation:** Hydroxide ion (OH^-) deprotonates the α -carbon of the ketone, forming an enolate intermediate.
- Retro-Aldol Cleavage:** The enolate undergoes a retro-aldol cleavage, breaking the C-C bond that formed the ring, resulting in an open-chain enolate intermediate.
- Protonation:** The open-chain enolate is protonated by water (H_2O) to form an enol intermediate.
- Enol-Keto Tautomerization:** The enol intermediate tautomerizes to form the final product, bicyclo[6.1.0]non-2-one.

Practice Problems

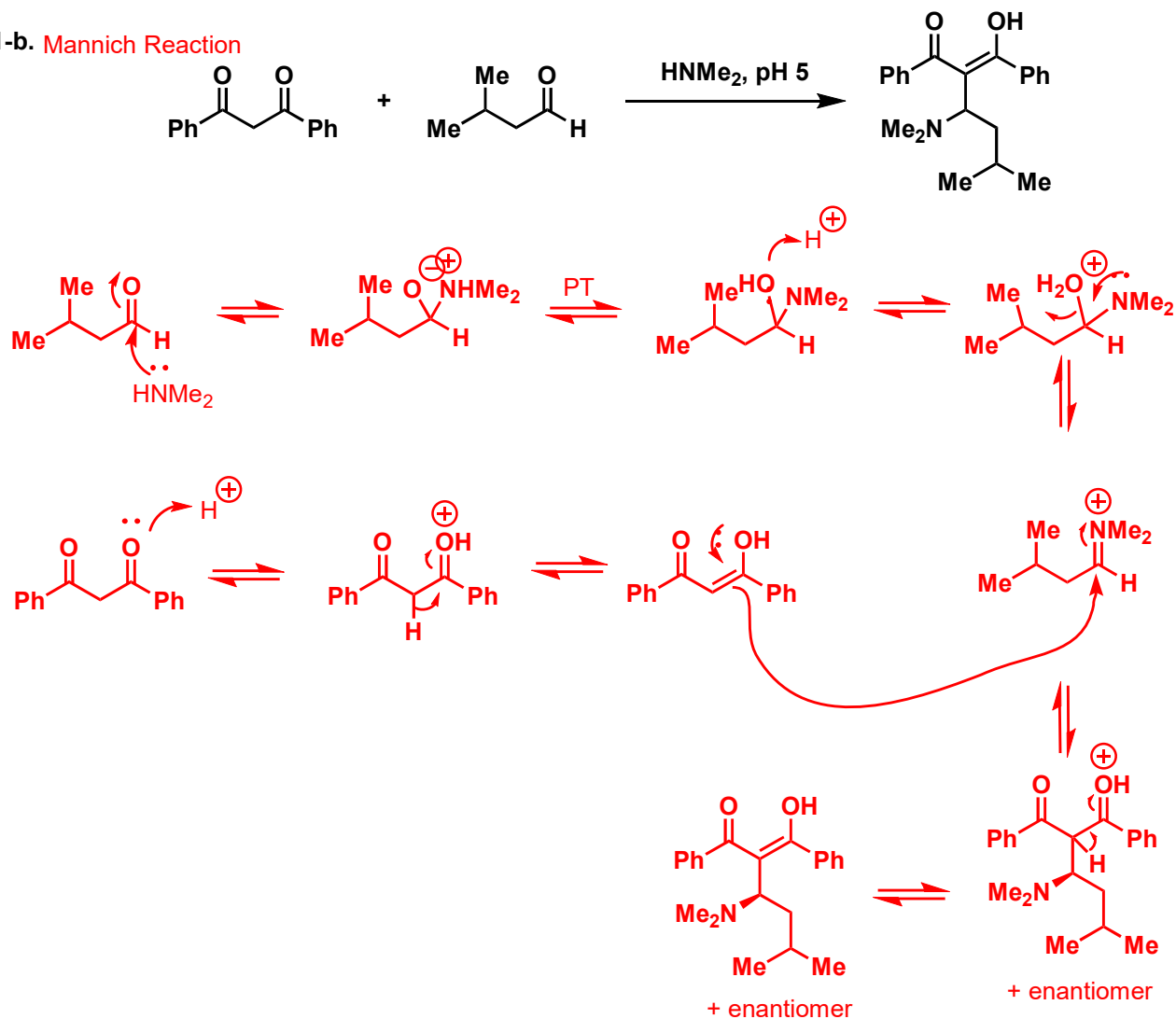
The following problems are included to help assist with your preparation for the final exam. The topics featured in the following questions will **not** be on Exam 3.

Skillbuilder Problem 1: Mannich Mechanisms

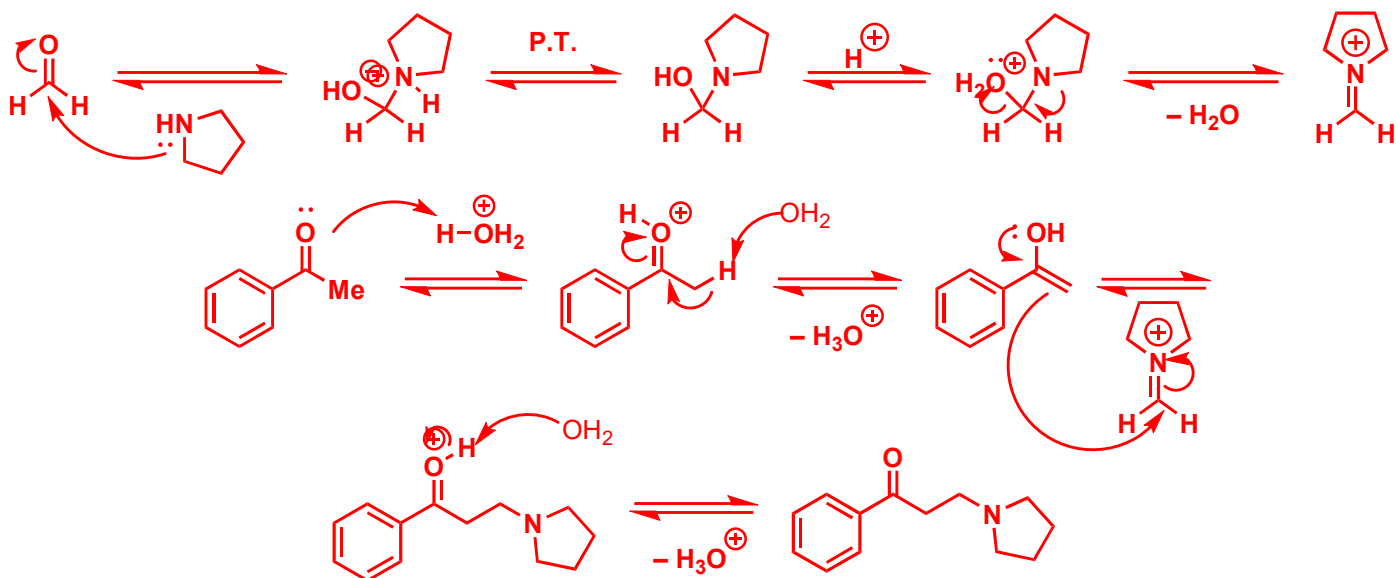
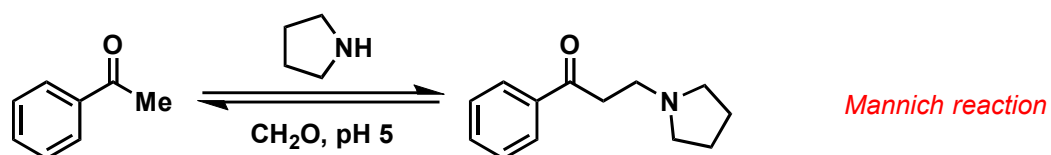
Propose a mechanism for each transformation, using curved arrows to represent the redistributions of electrons in each step. Consider the stereochemical outcomes of your reactions.



1-b. Mannich Reaction



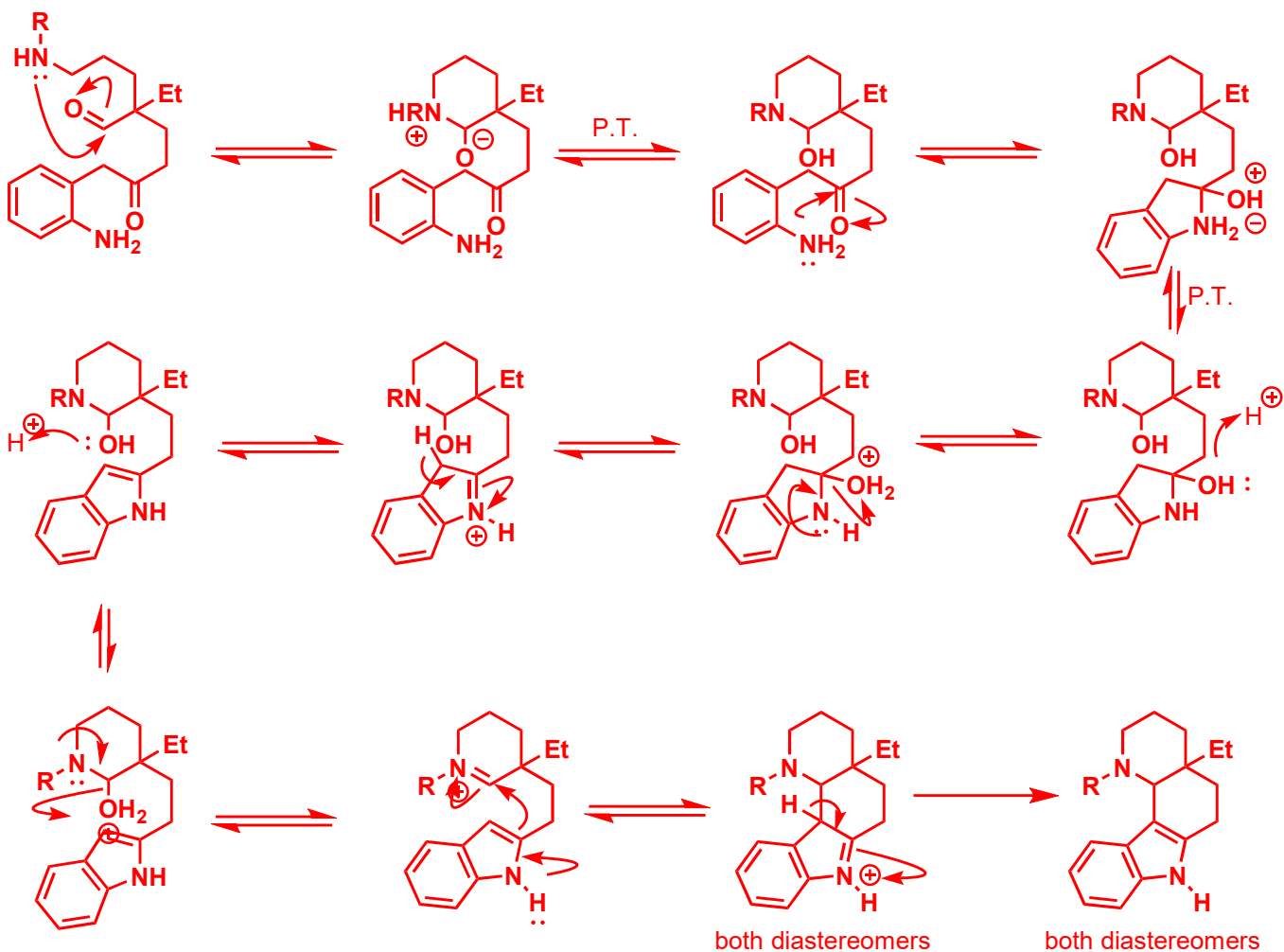
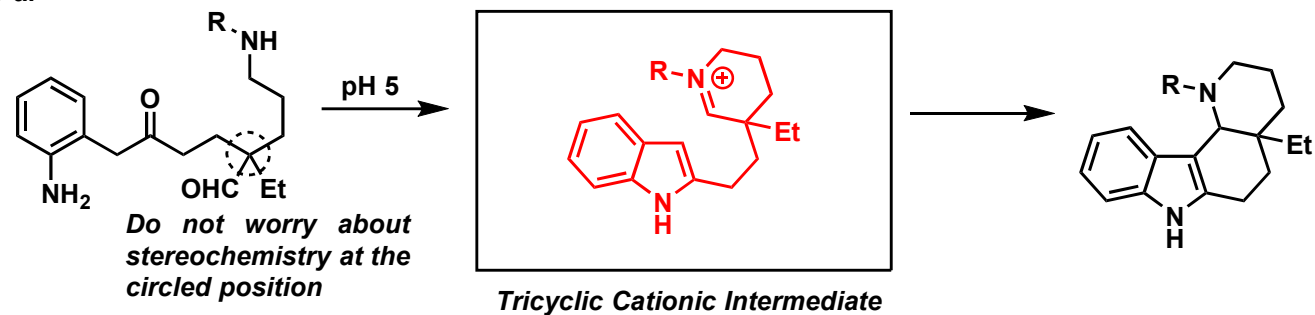
1-c.



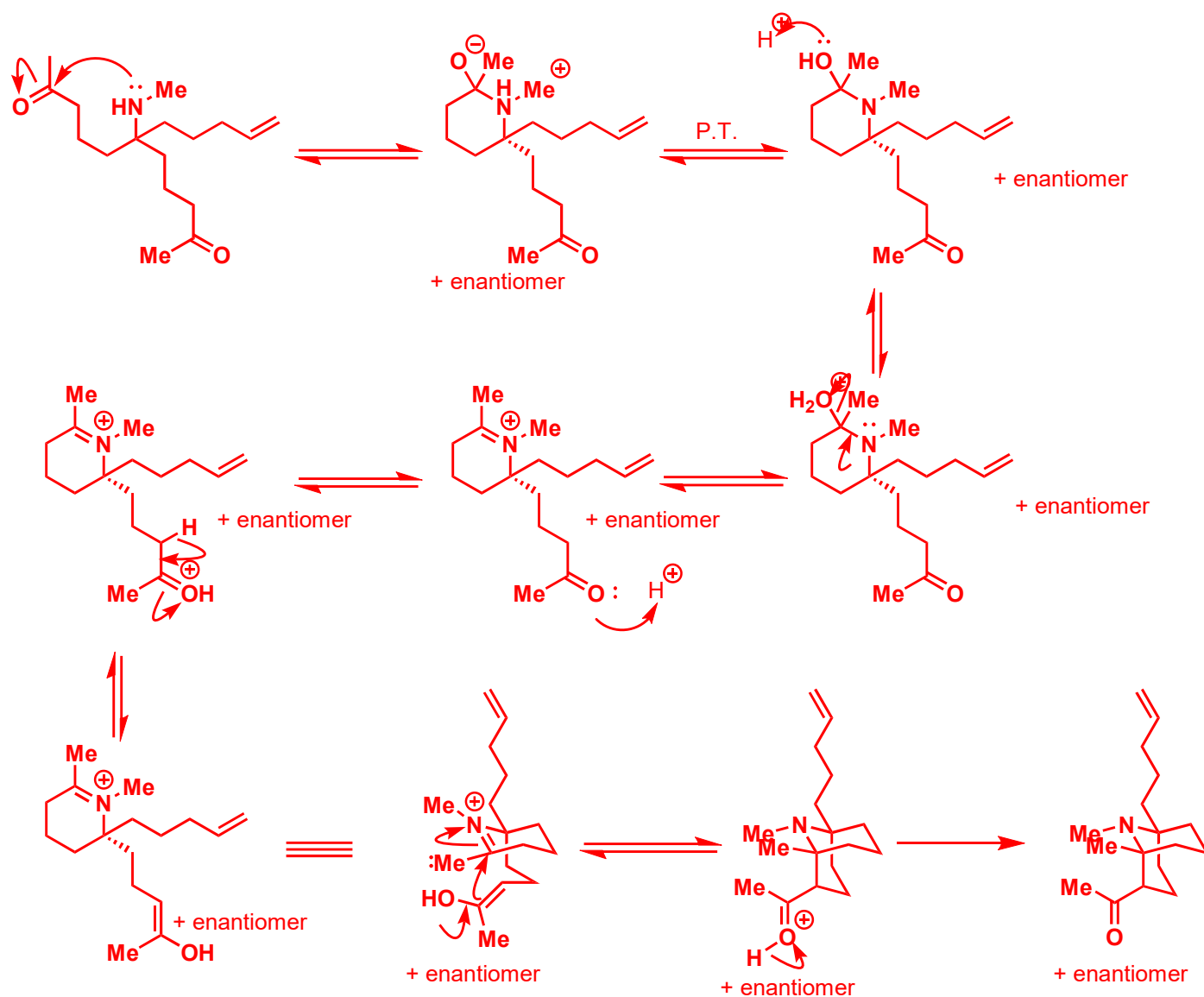
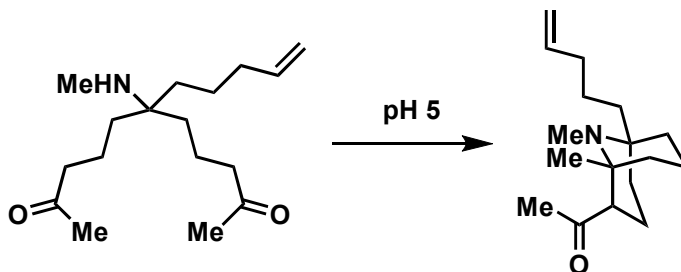
Challenge Problem 1: Mannich Mechanisms

Propose a mechanism for each transformation, using curved arrows to represent the redistribution of electrons in each step. Consider the stereochemical outcomes of your reactions.

1-a.



1-b. Mannich Reaction



1-c.

Mannich Reaction

